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PRESIDENT'S ADDRESS

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A YEAR AGO, as incoming president, I thanked you for the honor given me. The College, ever since its inception, has been an integral part of my professional life, but the past year has been the most memorable.

The president of any organization has the unique opportunity to see its inner workings; has to learn whether the aims and objectives are being carried out, whether the financial structure is sound, and whether the guidance is mature and stable.

We are a comparatively young organization as medical groups go. We might still be struggling for a foothold, but we are not. Our membership is growing steadily, our finances are sound, and our aims and objectives are being fulfilled. In looking back over the years of our existence, I credit our steady progress to the unusual "rapport" among us. None of our accomplishments would have been possible without the complete cooperation of all of the Fellows and members.

I am particularly proud of our brilliant postgraduate courses. Consistently, these are unexcelled in their arrangement, the speakers, and the papers presented. While these courses are slanted to the newer students in allergy, they are also appreciated as refresher courses by the veterans. If this were our single contribution to the advancement of allergy, it would, in itself, be a noteworthy one.

Each year our scientific session presents the newest concepts in allergy and presents them in an objective fashion, so that they can be assessed with an open mind. There will be controversial theories in our field as long as allergy continues to advance, and these need to be weighed carefully and without bias. The College accomplishes this purpose.

Presented at the Fifteenth Annual Congress of The American College of Allergists, Inc., San Francisco, California, March 18, 1959.

Our meetings are practical. We emphasize not only the scientific investigation but particularly the clinical application so that those attending the meetings will leave with valuable and stimulating ideas. I hope the College will always keep our programs on this level—scientific and practical.

I know from two years of close association with the Program Committee how exceedingly difficult is the arrangement of the postgraduate and scientific sessions. The quality of the programs is a tribute to the men and women who have given so greatly of their time and effort. This year we can thank Drs. Coleman Harris and Cecil Kohn for their year-long efforts to bring us the finest in education in allergy.

I hope the College will continue to encourage, in every way, the younger men—in education, as committee members, as speakers, and as executives. We should maintain our healthy balance of the mature and seasoned and the young and inspired.

I am pleased that our Women's Auxiliary supports our policy of encouragement. They deserve special mention for their program of awards for Associates, residents, and interns.

For the future, there are two objectives which I trust will be considered. The first, and most important as I see it, is more education in allergy. I covered this subject in an address given in February at Chicago. However, my views on the subject will, I think, bear repeating.

It is our obligation as allergists to see that allergy is given ample time in the curriculums of our medical schools. The physician will encounter the allergic reaction in every phase of medicine, and he should be able to recognize it in all its forms. Then, too, the medical student must be exposed to education in allergy if he is to consider it as a specialty. The need for more men in our field may not seem so acute now, but it can be expected to become very real in a few years.

Every branch of medicine is demanding more time in the medical school schedule, and allergy must not be shunted aside. It must assume its rightful place among the other specialties.

I would like to see a full-time instructor of allergy in each medical school. This would, of course, be a long-term objective, but perhaps we should use it as a goal toward which to work. Those of us who teach or hold clinics in medical schools can work toward this, individually. There is much we can do, by presenting the cause for allergy and the need for more education in allergy, thus strengthening our relations with the deans and professors of medicine.

The American College of Allergists can further this objective. I suggested a joint committee on education of the two societies of allergists, one which can set up a continuing survey of undergraduate and postgraduate education in allergy. The assembled data would be invaluable in furthering our educational program, and the committee could furnish assistance and information to the medical schools.

Allergy is undeniably related to every province of medicine, and there

is an overwhelming need for more knowledge and better understanding of allergic diseases among members of the medical profession at large.

The second objective which I consider quite vital is more and better information for the public. The public is entitled to know what we do and what we think. We may try to excuse our lack of public information on the grounds that our research is incomprehensible to the layman, but this is a weak excuse. We have any number of men in the College who can write authoritatively and well. There is no doubt in my mind that they could make interesting presentations to the public of any new developments, new theories, and new concepts in allergy. Allergic individuals avidly read anything concerning diagnosis and treatment of their disease. They are as interested as we are in advancements in allergy.

The point which disturbs me greatly is that there are so many articles on allergy which are not written by allergists. The popular magazines and the newspapers are full of information on allergy written by lay medical writers, endocrinologists, mothers of allergic children, psychiatrists, dentists and just about anyone who has anything to say about allergy. The exception is the member of our own specialty. Some of this published information is good, some is rather doubtful, and some of it is dreadful. It should be a challenge to us to see that the public receives information which is not only interesting but authentic. Let us see what we can do to counteract this flow of inadequate, and sometimes misleading, information.

There is little need for me to say more. I deeply appreciate the experience of this past year, and it is with great confidence that I put this responsibility into the competent hands of Dr. Cecil Kohn.

AVERAGES AND INCONSISTENCIES

"That this is so will be immediately apparent if we look at the problem through the spectacles of Claude Bernard. Let us therefore consider a fictitious situation. We may suppose: (1) that a disease D is incurable if untreated; (2) that a clinical trial of the usual type leads us to assess the recovery-rate under treatment A as about 25 per cent, and the recovery-rate under treatment B as about 50 per cent. In such circumstances we too easily then content ourselves with a recommendation to step up the recovery rate 25 per cent by substituting treatment B for treatment A. If so, our preoccupation with averages has blinded us to biological realities. If we are alert to the manifold interaction of nature and nurture, the outcome invites us to ask the question: what peculiarities are common to individuals who respectively respond or fail to respond to one or other treatment?"—LANCELOT HOGBEN, *Statistical Theory*. New York, W. W. Norton.

ALLERGY RELATED TO BRONCHIECTASIS IN CHILDREN

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BRONCHIECTASIS is not commonly diagnosed in children in spite of the fact that the respiratory tract is the site of frequent infections during early childhood. Respiratory disease due to allergic disorders has reportedly been increasing in the pediatric population.[1] This has been brought about by bacterial sensitivity of the young child due to infections within the family group, nursery school exposure, increased hot air heating of homes, air pollution, home building, soil cultivation, and viral diseases.

We have been impressed from patients observed that bronchiectasis is not uncommon in the pediatric group and that allergy is an underlying factor setting off this disease. It is the purpose of this paper to discuss the problem and present illustrative patient cases.

The term "bronchiectasis" applies to a pathologic process which, after a period of time, causes cylindrical or saccular dilatation of the bronchial or bronchiolar lumen. This is demonstrated in Figure 1. Gross[2] states that formation of exudate within a lumen, dilatation of the bronchioles, and inflammation in surrounding lung tissue can progress simultaneously, but they do not necessarily do so. Luminal suppuration can be marked and tissue reaction be minimal; or conversely, the bronchial exudate can be slight while the pulmonary tissue disease is extensive. It is possible to have great bronchiolar dilatation and yet reach a stage where there is little or no exudate in the bronchial tree and practically no consolidation of the pulmonary substance.

At times, pseudobronchiectasis[3] may exist, and this diagnosis is justifiable when subsequent visualizations of the bronchial tree reveal normal configuration of bronchi which were formerly dilated, and where fibrotic changes have not become irreversible.

Bronchiectasis is often overlooked because some children who are ill and undernourished have little sputum or cough, while others with a great deal of both may appear well and are full of energy. Antibiotic agents mask respiratory symptoms by reducing bacterial infection but abnormal physical and radiologic signs may persist for many months or years.

Figure 2 shows a microscopic section of saccular bronchiectasis of the lateral basal segment of the right lower lobe of lung. This child had very little cough, no hemoptysis, no rales, and was in excellent nutritional

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status. Sections of the dilated distal portion show a fibrous thickening of the bronchus and almost complete destruction of the muscle wall. There is a marked chronic inflammatory response with heavy lymphocytic infiltration of the parenchyma in the surrounding lung tissue.

Fig. 1. Gross section demonstrating bronchiectasis.

In the presence of respiratory disease due to allergy bronchial dilatation occurs. This can take place either by an inspiratory effort as in long-standing and recurring allergic bronchitis, or in the expiratory effort of bronchial asthma, or by traction upon the bronchial walls from without as seen following pneumonia. This dilatation[4] is associated with an increased production of mucin by the bronchial glands which, in turn, causes a rise in viscosity. The efficiency of ciliary propulsion is altered and accordingly, plugging and infection of the bronchi results.

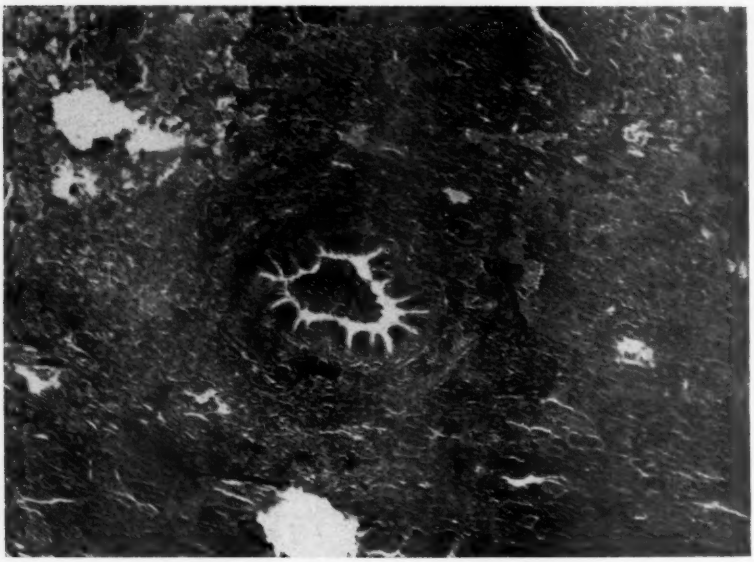

Fig. 2. Microscopic section of right lower lobe of lung demonstrating saccular bronchiectasis of the lateral basal segment.

Field[5] has reported that there are hidden cases of bronchiectasis in children with histories of recurrent coughs and colds, the true picture being revealed only in adult life, as when during adolescence, they lose practically all of their symptoms. Residua of incompletely cured pulmonary insults, be they caused by neonatal atelectasis, bronchiolitis, or pneumonia will cause spasm and swelling of the bronchial mucosa with narrowing of the bronchial airway. Associated with these pulmonary diseases the respiratory tract with known allergic disorders often will not give much symptomatology until the onset of bronchial irritation. In many patients the basic allergy is overlooked or neglected because of premature enthusiasm in antibiotic therapy and failure to obtain a detailed history.

Roentgenograms are not always satisfactory in revealing bronchial pathology, and often bronchoscopy will not be valuable in acute bronchial asthma. Bronchograms[6] are necessary for accurate diagnosis of broncopulmonary problems in infants and children.

Israels[7] has pointed out seven pathologic peculiarities in bronchograms of asthmatic patients. These are (1) spasm or swelling of the bronchial mucosa, (2) "flowers," a descriptive feature of the bronchi in which the acini of some are full of lipiodol, in contrast to the surrounding acini in which lipiodol is absent, (3) segmentation of bronchi, (4) nude filling defect, (5) fringes defect, (6) broken branches defect, and (7) bronchiectasis.

There is no contraindication to performing bronchography except in

an acutely ill child. At times, pathologic defects due to congenital anomalies of the tracheobronchial tree are diagnosed.

Paulson[8] states that embryonic defects are no longer considered primarily significant in the etiology of true bronchiectasis. There are, however, certain developmental abnormalities characterized by cyst-like formations of the bronchi which may simulate acquired bronchiectasis. Congenital cystic disease, appearing in the lungs because of failure of bronchial buds to develop to the point of differentiation into normal alveolar tissue, may become infected and produce the condition known as cystic bronchiectasis. The cystic and bronchiectatic areas in the parenchyma associated with intralobar broncho-pulmonary sequestration due to anomalous systemic arteries to the lung may likewise simulate acquired bronchiectasis roentgenographically and clinically.

We feel there is a need to perform bronchoscopic studies in all children with respiratory disease due to allergy to observe the nature of the bronchial mucosa, degree of inflammation, patency of segmental bronchi or occlusions, the presence of non-opaque foreign bodies, congenital defects, and to secure secretions for eosinophilia and bacteriologic study.

Three cases of bronchiectasis with underlying allergy are presented.

CASE REPORTS

Case 1.—P. K., a white girl aged six, developed a right lower lobe pneumonitis in July, 1955. On roentgen films of the chest there was an abnormal density in the right base overlying the leaves of the diaphragm. This pathologic process persisted after clinical cure (Figure 3).

Tuberculosis and cystic fibrosis were ruled out. A bronchoscopy was performed. The bronchial secretions of the right lower lobe had a very foul odor. The bronchi of both lower lobes, but particularly the right, showed dilatation, thickening and induration. The quantity of secretion present was small. There was no evidence of foreign body, ulceration or stenosis. Bronchograms showed a saccular bronchiectasis of the right lower lobe (Fig. 4). No abnormality was noted in the bronchial tree on the left.

Both maxillary sinuses were clouded and there was purulent secretion in the middle meatus and spheno-ethmoidal regions. The child had little cough, no hemoptysis, and normal nutritional status. A survey of allergies was carried out. From her history it was revealed that the patient had been sleeping next to a hot air vent with her cocker spaniel dog beneath the bed. A rhinorrhea was commonly noted by her mother; she also had an occasional cough especially when visiting her father's fur shop. On further investigation there was revealed mold in the basement where the child often played, and heavy ingestion of milk, eggs, bread and peanut butter. On skin testing there were shown positive reactions to these inhalants and foods.

Antibiotic agents cleared her sinusitis and hyposensitization treatment was administered for two years. Her weight kept in the seventy-fifth percentile on the Stuart chart and there was no cough, little respiratory infection, and no wheeze during this time.

In December, 1957, on roentgenograms there was still outlined an area of abnormal density in the right lower lobe. On repeated bronchograms there was revealed an advanced saccular bronchiectasis with little change in appearance over the original.

A right lower lobectomy was performed. At the time of the procedure, the segment

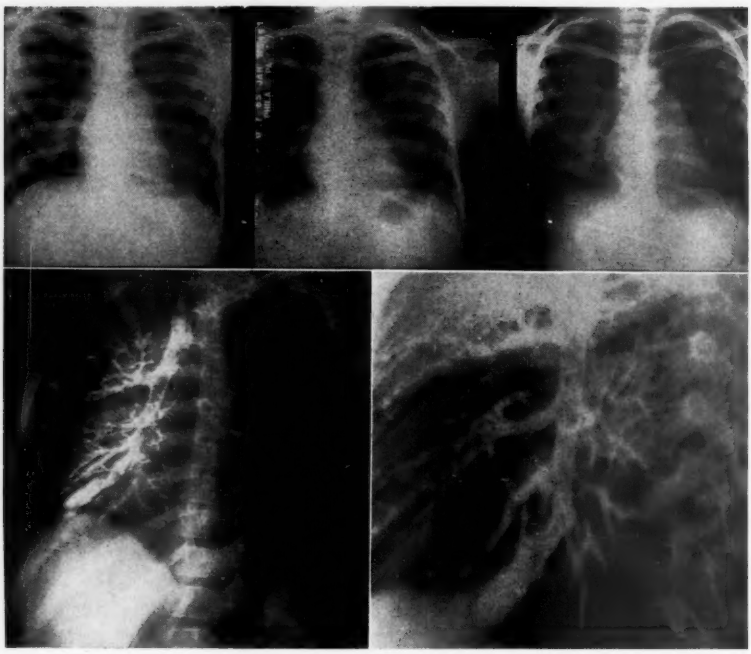

Fig. 3. *(Above)* Case 1 (P.K.) Roentgen films showing abnormal density in the right base of lung overlying the leaves of the diaphragm.

Fig. 4. *(Below)* Case 1 (P.K.) Bronchograms showing a saccular bronchiectasis of right lower lobe.

involved was atelectatic and tightly adherent to the anterior chest wall. The tracheobronchial tree of the resected lobe, when opened, led into a thick-walled saccular dilatation in the lateral basal portion of the lung. No gross pus was seen. Microscopic sections revealed a fibrous thickening of the wall of the bronchus and almost complete destruction of the muscle wall. The patient convalesced with no complications.

Case 2.—A. M., a white boy, aged eight, was admitted because of non-productive cough, wheeze, and weight loss. This boy had rhinorrhea since infancy, developed asthma at fifteen months of age, and, according to his mother, always had excess mucus in his nose and throat. A tonsilectomy and adenoidectomy was performed at five years of age. During the first three months there was colic, and during childhood, frequent respiratory infections.

At six years, survey of allergies was done and there were shown positive reactions to house dust, ragweed, barley, oats, corn, and orris root. Hyposensitization was instituted for one year without noticeable improvement. During this time he had been ingesting large quantities of eggs, peanut butter, and milk. On admission April, 1957, on roentgenogram of chest there was revealed some increase of the vascular markings in both lung fields, but no honey-combing, atelectasis or pneumonitis. Bronchography revealed a cylindrical bronchiectasis of the lateral basal segments of the left lung (Fig. 5). The examination of the right bronchial tree showed it to be essentially normal.

Tuberculosis, cystic disease and foreign body were ruled out. An electrophoretic study showed a definite hypogammaglobulinemia. There was hot air heating of the patient's home located in a damp area of New Jersey, and a dog lived in the home. On further skin testing there were revealed reactions to multiple foods and additional

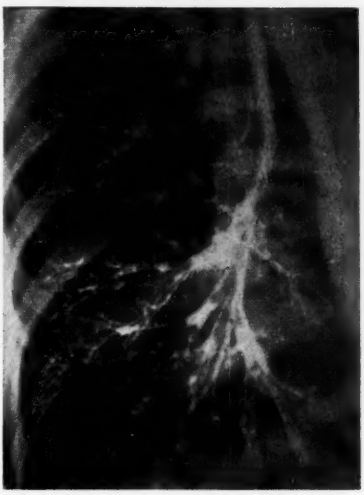

Fig. 5. Case 2 (A.M.) Bronchogram revealing cylindrical bronchiectasis of lateral basal segments of left lung.

inhalant allergens with strong reactions to dog dander and molds. Therapy for the past year has consisted of hyposensitization using multiple inhalant antigens, gamma globulin and autogenous vaccine.

The patient's diet was modified. A bronchogram was performed April 9, 1958, and there was shown a virtual disappearance of bronchiectasis with only a small cylindrical bronchiectasis of one lateral basal segment on the left (Fig. 6). The patient has been asymptomatic to the present.

Case 3.—A. B., a white boy, aged ten and a half years, was admitted because of cough, nasal congestion, and frequent respiratory infections. The child had eczema during the first three months of life. His father and an older brother have hay fever. At five years of age the child's tonsils and adenoids were removed because of mouth breathing and increasing frequency and severity of upper respiratory infections. Nasal congestion had become constant and he would cough and expectorate frequently. His appetite failed but he was normally active. Five months prior to his present admission, he was treated for sinusitis and pneumonitis. He has never had hemoptysis. The patient's stature was small and underdeveloped. His weight was less than the third percentile on the Stuart chart. On roentgenograms of the paranasal sinuses were shown a mottled infiltration and the right lower lobe of the lung had a mottled infiltration suggestive of bronchiectasis. On right lung bronchogram there was revealed a small area of bronchiectasis in the distal portion of the middle lobe, medially (Fig. 7).

Coagulase-positive staphylococci were obtained from the bronchial secretions. A moderate number of eosinophils were noted in smears of these secretions. A survey

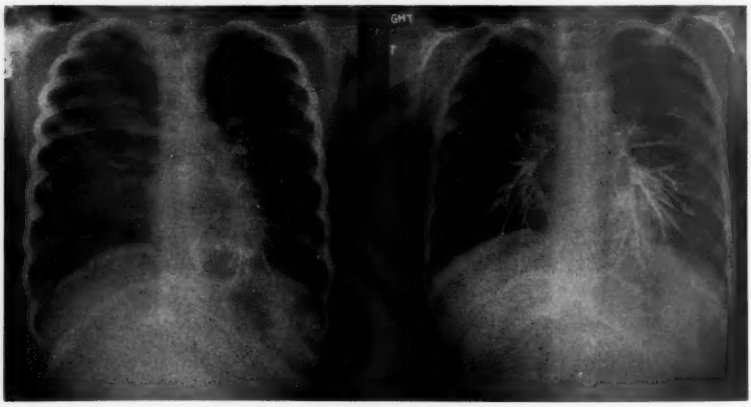

Fig. 6. Case 2 (A.M.). *(Left)* Bronchiectasis, April, 1957. *(Right)* Roentgen films, April, 1958, revealing virtual disappearance of bronchiectasis except for a small cylindrical involvement of one lateral basal segment on the left.

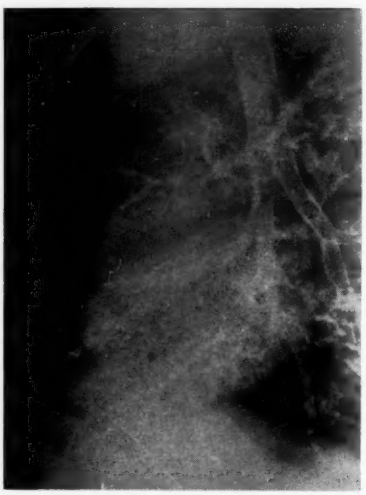

Fig. 7. Case 3 (A.B.) Right lung bronchogram revealing a small area of bronchiectasis in the distal portion of the middle lobe, medially.

of allergies showed the patient to react to trees, grasses, ragweed, dust, kapok, tobacco and horse dander.

Antibiotic therapy cleared his sinusitis. He was given hyposensitization for reactive allergens along with an outogenous vaccine. The patient has made mention of no complaints.

DISCUSSION AND SUMMARY

1. Bronchiectasis is not uncommon in children, and allergy is one of the factors setting off this disease.

2. The number of children with respiratory disease due to allergy is increasing in the pediatric population; they should be investigated for bronchiectasis.

3. Bronchiectasis is usually associated with chronic cough, expectoration and frequent respiratory infections. In children, these symptoms may be minimal or masked by premature enthusiasm in antibiotic therapy.

4. We feel that a "hidden bronchiectasis" occurs in allergic children which escapes detection because most clinicians are interested in treating the pneumonia, chronic tracheobronchitis, and sinusitis, and fail to treat the underlying allergy. A child with no cough, no hemoptysis and excellent nutritional status but with underlying allergy had a complete destruction of the muscular wall of a bronchus.

5. A plea is made for more bronchographic studies in children with respiratory disease caused by allergy to differentiate complications of allergy from congenital defects.

6. Three cases of bronchiectasis are presented in children who had different symptomatology and pathology, but all had underlying allergic respiratory disease.

7. Follow-up in selected cases revealed an ability to reverse bronchiectatic changes when adequate treatment for allergic disorders was instituted, and the patient was kept free of infection for a long time.

REFERENCES

1. Crook, W. G., Harrison, W. W., and Crawford, S. E.: The incidence of allergic disease in the general practice of pediatrics. J. Pediat., 52:20, 1958.
2. Gross, R. E.: The Surgery of Infancy and Childhood. Philadelphia: W. B. Saunders Co., p. 786, 1953.
3. Blades, B., and Dugan, D. J.: Pseudobronchiectasis. J. Thoracic Surg., 13:48, 1944.
4. Baker, J. M., Roettig, L. C., and Curtis, G. M.: The prevention and treatment of atelectasis by the control of bronchial secretions. Ann. Surg., 134:641-642, 1951.
5. Field, E.: Personal correspondence.
6. Ferguson, C. F., and Flake, C. G.: Bronchography in the diagnosis of pediatric problems. J.A.M.A., 164:518, 1957.
7. Israels, A. A., Orie, N. G. M., Geelen, E. E. M., Warringa, R. J., and Huizinga, E.: La bronchographie dans l'asthme. Les Bronches, 5:13-28, 1955.
8. Paulson, D. L.: Congenital factors predisposing to bronchiectasis. The Letters of the International Correspondence Society of Allergists, 21:72, 1958.

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Submitted May 5, 1958

It is more than likely that the annual global injury and number of deaths due to poisoning (excluding alcohol, hashish, opium and other addictions) exceeds by far the destruction which would be caused by an annual atomic bomb explosion in a heavily built-up area.—S. Locket, *Clinical Toxicology*, London, 1957.

PSYCHOSOMATIC GROUP THERAPY WITH PARENTS OF CHILDREN HAVING INTRACTABLE ASTHMA

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WE SHOULD LIKE to review one part of the problem concerned with the institutional care of children with intractable asthma. Specifically, it is part of the program under way in the Jewish National Home for Asthmatic Children in Denver, Colorado. Recovery and rehabilitation statistics have been reported previously to this society. As far as the psychotherapy of the children is concerned, it is considered possible to treat both parents and children in their own community. At present, however, with our limited knowledge, the time may be too long and the effort too great if the intractability of the asthma is considered. From a practical point of view, therefore, it was necessary to utilize the fact that removal of most of these children to a hospital ward interrupts the intractability of the asthma within seventy-two hours. It is generally known that hospitalization maintains the children in a non-threatening as well as in a non-allergenic environment. It was also observed both at the local hospital level and at the Denver institution that recurrence of the asthma often coincided with the visits of the parents.

We have, in a few words, outlined to you what took almost three decades to formulate and to implement in the Denver program. It was only later that it occurred to us that the relationship with the parent was largely involved in the intractable nature of the asthma and that separation or "*parentectomy*" (a word that we prefer to use because of its psychologic implications), led to improved results in treating the children. The more that was learned of the separation process, the more it appeared that rather prolonged periods of separation were required and that on the basis of the data obtained at the Institution, an eighteen to twenty-four-month period of separation and treatment was apparently optimal for more of the children. During this period of separation the asthma was treated from the point of view of both soma and psyche. That is, both the emotional problems of the children and their somatic therapies were included in the management procedures.

We know to a certain extent what happens to a child in Denver. For example, the conditions of group living and the nature of the identification process with older children leads to a special type of community. This

From the Jewish National Home for Asthmatic Children, Denver, Colorado.
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special community is characterized by an interesting development, namely —that the older children become psychotherapists for the newcomers.

As mentioned before, we have statistically significant follow-up data on the course of asthma in these children after they go home, but it is only in the last year that the authors have had the opportunity to study in detail the following features of the parental attitudes.

How do parents prepare the child to leave home to remain approximately two years in Denver?

What occurs within the home of the parents while the child is in Denver?

What happens when the child returns to his own home?

In the course of 100 parent discussion-group hours during the past year with the parents of children in the New York area, we have made 100 verbatim tape recordings of what transpired between the parents of the children at the Home in Denver and ourselves. May we briefly outline to you the organization of these parent discussion groups so that you may visualize what actually happens?

PARENT DISCUSSION GROUPS

Between twelve and fifteen parents are seen every Monday night for sixteen consecutive weeks. We see three groups each evening, with each group session lasting fifty minutes. Dr. Abramson's primary function is to orient the group along psychodynamic lines. Dr. Peshkin's primary function is to report specifically on the physical state of the children. These reports are based on personal monthly visits to Denver. However, in recent months, Dr. Peshkin has begun to participate more freely than hitherto in the psychologic discussions. The group was originally organized by a volunteer worker on the administrative level. The participants were charged according to their ability to pay—either nothing or up to $5.00 for each session. Our data show that even though people come from rather great distances, the attendance on the average was not dependent on whether the parents paid or not, that is, there was no correlation between the fee paid and the attendance record.

Verbatim recordings are made, transcribed, and are at present being studied. There is a remarkable feeling that one gets in seeing ten to fifteen persons, most of whom come as couples, of different races, religions and social backgrounds, cemented together by a common need—the need to take care of a sick child, a child sick with intractable asthma. We are sure you will know that group-therapy sessions of this type, having two group leaders, may develop into a complicated interaction between the two group leaders . . . in this case, the two authors. Fortunately, in the 100 sessions that we have had thus far, there has been healthy disagreement but no friction. We both feel that our disagreements on certain points have

stimulated free discussion within the groups and have given impetus to verbalization on points that otherwise might have remained hidden. We work all day Mondays. With little time for dinner, we meet with the groups from 7:30 to 10:30 in the evening. It was most surprising to us to discover that we were relaxed at the end of the evening. We feel that this relaxation on our part perhaps is connected with the fact that we have strongly identified with the needs of the groups and with a basic desire to discover the truth at a level of inquiry and understanding of the groups themselves. As we developed more insight into the needs of the groups, we learned we could eventually handle groups that were larger than twelve —up to sixteen or seventeen persons—provided that at least five of the couples present were husband and wife.

Once a month Dr. Peshkin reports on the physical condition of the children. On that evening, emphasis is placed on the physical nature of the allergic state. Parents take advantage of our understanding of the allergic process to become re-oriented in the case of their allergic child. (May we remind the reader that it is not the doctors that take care of the allergic child, but it is the parents. And it is they who must be instructed.) In addition, special letters are sent each month by the Home's psychologic counseling services to the parents. A more detailed report is sent to us.

A primary unit of therapy has been arbitrarily set at sixteen sessions for the group discussions, but we now have a graduate group that has had more than thirty-two sessions. At the termination of sixteen sessions, the parents are seen once a month to receive a report on the physical state of the children as previously mentioned. These reports are eagerly looked forward to by the parents.

We still adhere to the point of view that ordinary social service functioning is unsatisfactory from the point of view of the physicians, because we, the physicians, were not learning about the parents of these asthmatic children.

A preliminary inspection of our data indicates that we might, after content analysis of the data, be able to distribute information to physicians for their own use.

May we very briefly review some of the data obtained so far? Let us first take up how the parents prepare the child for separation from their homes. For example:

1. "Denver is the place where asthma can be cured."

2. "We don't want you to go to Denver, but you must go to get better."

3. There is conflict within the home . . . one parent is in favor of Denver, the other against Denver. In such cases the mother is usually not in favor with the father in favor of Denver. We have not as yet determined any difference in parental attitude as far as the sex of the child is concerned with younger children.

4. While preparing the child to leave for Denver, hostility may flare up between the parents, each blaming the other, or curiously enough, hostility is sometimes so

well screened by parents that each praises the other as a perfect parent, accepting the change which occurs in Denver as due to a "change in climate." These parents refuse to accept the point of view that emotional factors are involved and prefer to believe that any improvement is on a purely physical basis.

Most of the parents come to the sessions with an underlying resentment toward doctors. Nearly all have been told, initially, by the pediatrician or family physician that their children would probably outgrow the asthma. This resentment and search for information on the part of the parents led us to learn that group psychotherapy cannot be successfully conducted unless the psychotherapist is prepared to deal with the pharmacologic and immunologic aspects and controversies regarding the various types of asthma. He must be able to deal with the orientation of the group successfully along body-mind lines. Similarly, the allergist must be oriented in elementary psychodynamics.

While the child is in Denver he is taken care of medically, sociologically and psychologically. The child is treated as an individual as well as a member of a group into which he is integrated along many lines—interpersonal relationship to other children, to adults, to school, group play and competitive sports, among other activities. Our data, however, show that the parents are usually in a constant turmoil of anxieties and hostilities toward: (1) one another, (2) the child, (3) the siblings, (4) the grandparents, (5) the administration of the Institution, (6) the local doctors and the doctor at the Institution, (7) the house parents at the Institution, (8) the counseling service at the Institution, (9) and finally toward the authors, but less frequently than we had anticipated, except in the case of the fathers comprising the group.

Five of these men were definitely and overtly hostile and introduced an interesting phase of psychotherapy in the group. Women verbalized more frequently in the beginning. Men verbalized later, often with less hostility while offering pertinent suggestions. The few parents who dropped out usually did so because their home unity was threatened by the discovery of the psychologic factors.

A unique feature of the group therapy sessions was the knowledge we obtained about Denver from telephone conversations of the children with their parents. Distortions were manifested by over-emphasis, underemphasis and expectancy of ideal function of the Institution. We were thus able to get a realistic perspective on the functioning of the Institution.

Parents were disturbed by the child's initial loneliness. Children who had experienced frequent hospitalization were less lonely than children who had not. Part of the job of the therapist was to guide the parent through the intricacies of dealing with such problems as: concern about the child's sense of being unloved, rejected, a sense of loneliness and the child's complaints about other children, the infirmary, the school, and so forth.

When the child's asthma becomes worse at the Institution we believe

it may happen in two ways which will interest us here. The child may identify the Denver Home with his own home. Then the child has to be separated from the Denver Home. In other cases, fear of going home was connected with the dangers attendant upon adjusting to school and new friends and probably to the parents, themselves. Children feared the disruption of a school term. We also learned that prior to coming to Denver some of the children had educational defects because of illness and relative emotional immaturity. These defects were found in their learning to spell, read and write. These basic deficiencies in the education process often led to failure in other subjects. This threat of failure frequently led to exacerbation of asthma.

A word of caution about the parents receiving psychotherapy outside of the group framework. In a few cases this has produced confusion because of disagreement with the group leaders. It is very important to realize that the majority of parents do not have children with primary behavior disorders. When the asthma in these children cleared they did not reveal behavior problems. However, a small group of children after being cleared from asthma evidenced various kinds of behavior problems, characteriologic disorders including delinquency. It is this group of children whom we believe had a masked primary behavior disorder and this masking occurred because the children were immobilized by their intractable asthma.

PARENTAL VISITS TO DENVER

Let us now describe the impact upon the parents of a first visit to Denver and subsequent visits which are spaced at six-month intervals.

1. If the child is free from asthma and receiving no special treatment, parents are pleased, but they are also bewildered because the evidence of the effectiveness of parentectomy arouses unconscious guilt feelings which emerge only later during the group sessions. In this group there is also a feeling on the part of the parents of inadequacy based on being unable to handle effectively the child's emotional problems.

2. If the children are still wheezing even though functioning well, the parents are appreciative but disappointed that their children have not recovered as much as the group that had no wheezing. Some of the parents were apparently unconsciously pleased that the children were not completely relieved from asthma.

3. In the "hard core" cases where the improvement is negligible, the parents are outwardly frustrated. Such frustration is caused by ambivalence between the need for a cure and the need for vindication as loving parents.

The first Denver visit of the parents is a threat both to children and parents. This threat decreased during subsequent visits and any asthma occurring during a parent visit decreases as time goes on.

The children have to be carefully prepared for separation from the Institution, but nearly all of the parents were concerned with their own attitudes toward having their children return home. Fears of the parents were based upon:

1. The possibility of asthma returning in the child.
2. The possibility of being unable to cope with newly developed maturity in the child. This is tantamount to the fear of having the child acting as a stranger in his own home.
3. The possibility that the healthy child might regress and force parental regression to an earlier relationship.
4. The dislike of having the child disrupt the essentially new life which developed during the absence of the child.
5. Unknown fears which control their dislike of having the child return at all.

CONCLUSION

In conclusion, we have described for you the scope of the problem with which we had to cope in the creation of the group therapy sessions with the parents of intractable asthmatic children. We have described some general psychological phenomena encountered in these group sessions and the methods we have improvised in the management and orientation of the parents. We know that as a result of the parent group discussions a valuable adjunct not only to therapy but also to our future knowledge of the basic mechanisms will develop. Our findings may lead to improved treatment for anxious parents of intractably asthmatic children not only at the institutional level but also in the child's home.

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Submitted May 15, 1958

DETERMINATION, HOPE AND SUCCESS

" 'You can undertake without hope and persevere without success.' Thus may speak an inflexible will, or honor and duty, or a nobleman with a noble cause. This sort of determination, however, would not do for the scientist, who should have some hope to start with, and some success to go on. In scientific work, it is necessary to apportion wisely determination to outlook. You do not take up a problem, unless it has some interest; you settle down to work seriously if the problem seems instructive; you throw in your whole personality if there is a great promise. If your purpose is set, you stick to it, but you do not make it unnecessarily difficult for yourself. You do not despise little successes, on the contrary, you seek them: *If you cannot solve the proposed problem try to solve first some related problem.*"—G. POLYA, on Descartes, *How To Solve It*, Garden City, New York, Doubleday and Company, Inc., 2nd edition, 1957.

RICE INTOLERANCE IN INFANTS: MASKED FOOD ALLERGY?

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THE present paper describes the results of a study that originated with the chance observation of an infant who developed a syndrome resembling what Randolph[2] termed "masked food allergy" or "food addiction." It appeared to be the result of feeding infant rice cereal.

The purpose of this study was (1) to determine the incidence of this rice intolerance in a specific experimental population, (2) to enumerate its clinical variations, and (3) to evaluate the role of allergy in this condition.

METHOD

The experimental population was drawn entirely from the author's private practice, which consists of 75 per cent allergic infants and children and 25 per cent non-allergic infants, some of whom are off-spring or siblings of allergic individuals. The mothers of all infants in the author's practice under six months of age were asked about the presence of "colic" or "excessive hunger." In each such instance the mothers were asked to withhold cereals for one week, and then to reintroduce the same cereal. They were urged to use only rice cereal as the first solid food offered the child. This was usually introduced between the ages of two and ten weeks, the average time being four weeks. Each mother was questioned about the incidence of major allergies in the child's family.

The criteria for the diagnosis of rice intolerance were the alleviation of symptoms such as excessive hunger, "colic," rhinorrhea, et cetera, when the cereal was removed from the diet and re-appearance of symptoms with the re-introduction of the food. Each child was skin tested with extracts of rice, wheat, oat and milk. Search for symptoms of rice intolerance were made only in infants under six months of age.

CLINICAL OBSERVATIONS

In general, the most characteristic complaint of parents was an expression of concern lest their infant not be getting enough food in spite of the fact that most such infants were gaining at a normal or excessive rate. In no instance did a mother suspect the cause of the symptoms until she either accidentally discovered it herself or it was suggested to her by the author.

The following three case histories have been selected as representative of this problem.

REPORT OF CASES

Case 1.—P.D. was first seen by the author at five months of age because of incessant crying and excessive hunger. There was a strong bilateral family history of

major allergies. At four weeks of age he had developed abdominal discomfort and diarrhea, which was promptly relieved by changing his formula from evaporated milk to a soybean preparation. At six weeks of age, rice was introduced into his diet. His mother noted that in the following weeks he became increasingly "hungry" with frequent crying which seemed temporarily relieved when feeding him. By this time additional solids had been introduced into his diet. His "colicky" discomfort increased in severity and he wanted to eat more frequently. He gained weight "very well" and had no nasal discharge, emesis or diarrhea. By the time the child was five months old, the parents were frantic because of the child's severe colic and the apparent hunger night and day.

Because of the family history of allergy and the infant's previous history, which suggested the possibility that he had had milk allergy at four weeks of age, the mother was advised to put the child on an "elimination diet." She warned the author that the diet must not be too restrictive in calories, since her five-month-old infant was so hungry. Consequently, the infant was placed on an elimination diet recommended by Glaser,[1] consisting of Mullsoy, lamb, apple, carrot and rice. There was no improvement in his condition. A more restrictive diet of Mullsoy and rice was then tried, again with no improvement. While the child was on this diet, his mother reported that over a weekend her supply of rice was exhausted. She noted, to her surprise, that his "hunger" dramatically subsided and for the first time in months he had no colic or crying for twenty-four hours. The following Monday, she obtained more rice because she did not suspect that this food bothered her child, and because she expected his hunger to recur unless he got "enough" food. Within half a day of re-introducing rice into the infant's diet, he again became very irritable, cried excessively and wanted to eat frequently. Rice was permanently removed from his diet with prompt subsidence of his symptoms. At the time of this writing the patient is six years of age. He and a sibling have developed perennial allergic rhinitis and mild pollinosis.

Case 2.—E.K. was studied from birth for routine well baby care. Both his parents have major allergies and three siblings have mild perennial allergic rhinitis. The infant was breast fed for three months. At two weeks of age, the infant's appetite seemed to increase somewhat. A complementary feeding of infant rice cereal diluted with sterile water was recommended to decrease his hunger and enable the mother to continue nursing. Within two weeks the mother reported that the infant's hunger and crying had markedly increased to a degree that she presumed that her supply of breast milk was perhaps now inadequate. She was encouraged to continue nursing her infant. The infant became increasingly irritable and seemed hungry at shorter intervals after meals than formerly. Despite the fact that the child was gaining weight rapidly, his mother insisted that he must not be getting enough to eat. At about this time she ran out of rice cereal over a weekend. The following Monday the mother phoned to report that she had observed an apparent enigma. In spite of the fact that her child ate nothing but breast milk for two days his "hunger" had dramatically decreased to a point where the mother felt breast milk alone satisfied him. When rice cereal was introduced, his "hunger" and "colic" recurred. Elimination of rice from his diet resulted in an end to his symptoms. In the ensuing three years, the child has developed minimal perennial allergic rhinitis.

Case 3.—B.S. was studied from birth for routine well baby care. There was strong bilateral history of major allergy. At three and one-half weeks of age, his evaporated milk formula diet was augmented with pre-cooked rice cereal to satisfy a gradual increase in his appetite. After two to three weeks on this diet, his "hunger" seemed to increase so markedly that he was "demanding" feedings every two and one-half to three hours. He became more irritable, passed much gas per rectum and

slept fretfully. Three weeks after rice had been introduced, he developed nasal stuffiness with a clear watery nasal discharge. A smear of the nasal discharge revealed a marked eosinophilia. At this time, suspecting the possibility of rice intolerance, the author suggested withholding rice from the infant's diet. Within twenty-four hours the irritability, hunger and "colicy crying" decreased. The next day the nasal stuffiness decreased, entirely disappearing the following day. A week later rice was deliberately reintroduced. The symptoms of "excessive hunger and colic and rhinorrhea" returned.

RESULTS

Table I summarizes the incidence of symptoms attributed to rice intolerance observed in this study.

TABLE I. SYMPTOMS OF RICE INTOLERANCE IN TWENTY-FOUR INFANTS

Symptom	*Incidence*
Increased hunger	16/24
"Colic"	16/24
Rhinorrhea	3/24
Cough	2/24
Wheezing	1/24

Rice intolerance was found in 14 per cent (22/57) of infants with a positive family history for major allergic disease, as compared with an incidence of 2.6 per cent (2/75) of infants with no family history of allergy. Of twenty-eight infants seen by the author for treatment of major allergies during the period of this study, 14 per cent (4/28) exhibited symptoms of rice intolerance.

Scratch and intradermal skin tests for the presence of reagins to wheat, rice, oat and milk in the twenty-four infants with symptoms of rice intolerance resulted in positive reactions to rice in two infants, to oat in one, to wheat in four and to milk in three infants. Similar tests on fifteen normal infants without family history of allergy resulted in one positive reaction to rice and one to wheat.

At the time of this writing six of the twenty-two infants with symptoms of rice intolerance and with positive allergic family histories have developed perennial allergic rhinitis. Two have asthma, and one, pollinosis.

DISCUSSION

Slobody[4] estimated from a survey of the pediatric literature that the incidence of rice sensitivity is approximately one case to 300-450 normal mixed population. In children, he estimated it to be higher, namely one in 170-240. In his own study of 174 unselected children, he failed to uncover any case of intolerance to cooked rice, based on intradermal skin tests and ingestion of cooked rice. It may be that his experimental population was not large enough, since from his own review of the literature one would expect that his study would have to include between 170 and 240 children to find a single case. When he skin tested for rice sensi-

tivity, he did find erythematous wheal reactions greater than 2 cm. in diameter in two older children, and smaller doubtful skin test reactions in six other children between the ages of four and sixteen. Another possible explanation for his failure to uncover clinical evidence of rice intolerance is that his method of test feedings did not follow the technique for exposing latent or masked food sensitivity as recommended by Rinkel, Randolph and Zeller.[2] He did not indicate how many young infants were in the group studied. The incidence of positive family allergic histories was not mentioned.

The observations of this study point out that a food like rice, which is ordinarily thought of as being of low allergenicity potential, may cause clinical symptoms of intolerance.

Future revisions in textbook descriptions[1,3] of the technique for prescribing "elimination diets" should make clear the logic and details of avoiding the most common pitfalls in dietary manipulations of allergic children. If an infant's symptoms are thought to be caused by a food intolerance or allergy, the logical approach would be to begin by eliminating all potentially offending foods. In young infants this is impractical. Consequently, one should start the new test diet with a single food, regardless of the age of the patient. This one food should ideally be a rarely eaten food of low potential allergenicity. Unfortunately, even this approach might fail if the one food chosen happens to be one to which the child is sensitive. If the one food, given in as large quantities as the child desires, does not cause symptoms within three to four days, one additional food may then be added every three to four days until symptoms reappear. Appreciation for the nutritional needs of infants should dictate the choice of foods to be introduced. Some sort of vitamin substitution must be started within ten days of the onset of the trial diet, so as to avoid vitamin deficiencies in young infants.

For infants with masked food allergy, Rinkel and Randolph[2] have recommended so-called "individual food tests" as one way of demonstrating the offending allergen.

In any case, to eliminate certain foods while permitting the consumption of other potentially allergenic foods (such as rice), does not constitute a logical "elimination diet." It can only lead to confusion for both parent and doctor.

Whether the symptoms of "rice intolerance" in this report were truly allergic in nature is certainly open to question. That they occurred five times more frequently in children with family histories of allergy than in infants from non-allergic families may suggest the possibility that their intolerance was on an allergic basis. Skin testing was apparently of little help in settling this point. The subsequent development of major respiratory allergies in eight of the twenty-three infants with symptoms of rice intolerance was of interest.

CONCLUSIONS

1. Symptoms of rice intolerance were observed in 14 per cent of 157 infants of allergic families under six months of age and in 2.6 per cent of seventy-five infants of families with no known history of major allergy. These symptoms consisted of increased hunger, and "colic" in two-thirds of the infants. Some also had rhinorrhea, cough and wheezing.

2. Of twenty-eight infants less than six months of age who were under treatment for major allergies seen during this study, 14 per cent had rice intolerance.

3. Eight of the infants with rice intolerance subsequently developed major respiratory allergies within three years.

4. Only two of the twenty-four infants with rice intolerance had positive scratch or intradermal skin test reactions to rice extract.

REFERENCES

1. Glaser, Jerome: Allergy in Childhood. p. 463. Springfield: Charles C Thomas, 1956.
2. Rinkel, H. J., Randolph, T. G., and Zeller, M.: Food Allergy. Springfield: Charles C Thomas, 1951.
3. Rubin, Mitchell: Neison's Textbook of Pediatrics, Sixth Edition. p. 1446. Philadelphia: W. B. Saunders Company, 1957.
4. Slobody, L., Untract, S., and Hertzmark, F.: Rice sensitivity in children. Arch. Pediat., 65:182, 1948.

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STATISTICAL CORRELATION, CAUSAL AND COINCIDENTAL

"The first thing that has here to be regarded is that what we have in view when we speak of a cause is always an *operative agent;* and of course it follows that neither location in space (for this is a *status*) nor location in time (for this is also a *status*) admit of being called causes.

"There is here some confusion of thought; for we sometimes speak of the *effects* of distance, and more often of the *effects* of time. But that is a mere misapplication of words. For when we talk of time producing certain *effects* all we really mean is that the passage of time brings out more and more clearly the results of all the various causes which are at work around us. But the last and most important point to appreciate in connection with the discrimination of a purely coincidental and a causal statistical correlation, is that it is never anything in the statistics themselves which distinguishes mere coincidence from cause. It is always something extrinsic that does; and when we say that statistics show that two phenomena are causally related, we mean only that they confirm an inference which was established by crucial experiments, or was suggested by *experientia vega,* backed up in each case by 'contesserative reasoning' which tells us that a casual correlation is in one case *likely* and in another *inconceivable."*—Sir Almroth Wright, *Alethetropic Logic,* Wm. Heinemann, London, 1953.

THE USE OF DEXTRO-CHLORPHENIRAMINE (POLARAMINE®) IN PRURITIC DERMATOSES

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OUR experience with chlorpheniramine maleate (Chlor-Trimeton®) in the treatment of pruritic diseases of the skin was reported previously.[1,2,3] Since this type of disorder usually occurs on an allergic basis, characterized by the release of endogenous histamine, treatment with an antihistaminic agent produces a favorable response in most patients. Recently the dextrorotatory stereoisomer of chlorpheniramine was separated from the racemic compound[4] and made available for clinical trial. We wished to evaluate this new form, Polaramine®, in a similar group of office patients and compare it with Chlor-Trimeton for effectiveness and side actions.

PHARMACOLOGY

Polarization verified the fact that chlorpheniramine possessed the asymmetric organic molecule which is essential for optical activity and was therefore separable into its stereoisomers. In many separable racemic compounds, the stereoisomers, although identical structurally, demonstrate different degrees of therapeutic activity. When chlorpheniramine was separated into its dextrorotatory and levorotatory components, it was found that therapeutic activity resides almost entirely in the dextro isomer although toxicity is equal or greater in the levo isomer. It therefore seemed likely that on a weight-for-weight basis the dextrorotatory component of chlorpheniramine would be twice as potent but no more toxic than the parent compound. Studies of the potency[5] and toxicity[6] of Polaramine® in laboratory animals verified this hypothesis. Since Chlor-Trimeton was previously shown to be effective and markedly nontoxic,[7] the greatly increased therapeutic ratio of Polaramine® is especially noteworthy. Results of preliminary clinical trials with Polaramine® tended to confirm the laboratory data.[8]

METHOD

Two groups of office patients with pruritic skin disorders (Tables I and II) were selected for this study of Polaramine®.* The first group of eighty patients, ranging in age from six to eighty-two years, received the 2 mg tablets four times daily, postprandially and before retiring. The second group of 104 patients, ranging in age from ten to eighty years, received a 6 mg Polaramine Repetab after breakfast and another before retiring.

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*The Polaramine used in this study was provided by George Babcock, Jr., M.D., of the Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

TABLE I. RESULTS OF TREATMENT WITH POLARAMINE® 2 MG. TABLETS

Diagnosis	Number of Patients	Excellent	Good	Fair
Contact dermatitis	36	24	9	3
Circumscribed neurodermatitis	22	15	4	3
Pruritus, generalized or anogenital	10	6	3	1
Atopic eczema	6	4	1	1
Urticaria	4	2	1	1
Lichen planus	2	2	—	—
Summary	80	53 (66%)	18 (23%)	9 (11%)

Adjunctive therapy in both groups consisted of application of a mild, soothing ointment containing 40 gm 2 per cent boric acid solution, 40 gm lanolin or Aquaphor®, and white petrolatum 20 gm. When there was exudation we prescribed 2 per cent boric acid solution or 5 per cent Burow's solution. Patients were advised to limit consumption of coffee, tea, alcohol,

TABLE II. RESULTS OF TREATMENT WITH POLARAMINE REPETABS

Diagnosis	Number of Patients	Excellent	Good	Fair
Contact dermatitis	45	32	11	2
Pruritus, generalized or anogenital	26	16	7	3
Circumscribed neurodermatitis	17	10	4	3
Atopic eczema	8	5	2	1
Urticaria	5	3	1	1
Lichen planus	2	1	1	—
Psoriasis	1	—	1	—
Summary	104	67 (64%)	27 (26%)	10 (10%)

seasonings, spices, and citrus fruit juices. The importance of sufficient rest and relaxation was stressed. Ordinary soap was forbidden and patients were instructed to cleanse the skin with mineral oil or Lowila Cake.® No injections of antihistaminic agents were given during the course of the study. Patients were examined weekly.

RESULTS

The most significant effect of Polaramine® was the marked relief of pruritus, the most distressing symptom in the patients studied. Excellent or good results (total or substantial relief of itching) occurred in 90 per cent of the 184 patients treated with the tablets or Repetabs (Tables I and II). Control of the vicious cycle of itching and scratching usually was obtained with four tablets or two Repetabs every twenty-four hours. A few patients who had suffered for months with severe pruritus initially required three Repetabs every twenty-four hours. After approximately one week of therapy, dosage was usually lowered and eventually discontinued.

Relief of itching was followed almost invariably by improvement in the physical manifestations of the dermatoses and exudation was markedly

diminished. Scratching the lesions exacerbates and prolongs pruritic dermatoses and therefore control of pruritus is a primary goal of therapy. When this has been accomplished, the search for etiologic agents (often a difficult and time-consuming process) can begin.

Many patients reported that they had never felt so well; they preferred Polaramine® to all other therapies. Severely afflicted patients reported that sleep was no longer disturbed by itching, and a few others wondered if the new drug contained a tranquilizer.

Polaramine® appears to be considerably more potent than Chlor-Trimeton. Generally, we prefer the Repetab form to the standard tablet because of the former's convenient administration and rapid, prolonged activity.

There were no side effects which required interruption of therapy or reduction of dosage, even in patients who received the drug for as long as two or three months. None of our patients complained of the drowsiness which occasionally accompanies administration of other antihistaminic agents.

SUMMARY

Polaramine®, in 2 mg tablets or 6 mg Repetabs, was administered to 184 patients with acute or chronic pruritic disease of the skin. A mild ointment was also used, and a modified diet recommended. Prompt, sustained relief of pruritus was obtained in 90 per cent of the patients and was followed by objective evidence of healing.

Polaramine®, which is the destrorotatory stereoisomer of chlorpheniramine, appears to be considerably more effective than the racemic compound. The optimal dosage is four of the 2 mg tablets or two of the 6 mg Repetabs every twenty-four hours; the latter dosage is preferred. When improvement occurs, dosage can be reduced and eventually discontinued. None of the patients exhibited drowsiness or other untoward effects, and there was no evidence of toxicity or intolerance.

It is concluded that Polaramine® is an efficient and safe agent for treating pruritic dermatoses.

REFERENCES

1. Lackenbacher, R. S.: Chlor-Trimeton maleate repeat action tablets in the treatment of pruritic dermatoses. Ann. Allergy, 10:765-769, 1952.
2. Lackenbacher, R. S.: Oral and injectible chlorprophenpyridamine maleate (Chlor-Trimeton® maleate) in the treatment of pruritic dermatoses. Illinois M. J., 108: 14-15, 1955.
3. Lackenbacher, R. S.: Treatment of pruritic dermatoses with chlorpheniramine and prednisone in combination (Metreton). Ann. Allergy, 15:409-413, 1957.
4. Walter, L. A., and Kennedy, C.: Report to the Schering Corporation, 1958.
5. Roth, F. E., and Govier, W. M.: J. Pharmacol. & Exper. Therap., in press.
6. Cronin, M. T. I., and others: Report to the Schering Corporation, 1958.
7. Labelle, A., and Tislow, R.: Studies on prophenipyridamine (Trimeton) and chlorprophenpyridamine (Chlor-Trimeton). J. Pharmacol. & Exper. Therap., 113:72-88, 1955.
8. Babcock, G., and Packard, L. A.: Clin. Med., in press.

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THE TREATMENT OF ALLERGY TO RAGWEED POLLEN BY MEANS OF A SINGLE ANNUAL INJECTION OF EMULSIFIED POLLEN EXTRACT. VI.

Discussion of Results, Relationships and Some Miscellaneous Factors

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DURING the year 1958, I treated 1,029 patients suffering from disorders caused by allergy to ragweed pollen. Of these, 344 received either at my hands, or under my direct supervision, standard pollen extract prepared in saline[1] and given according to the multiple visit type of injection program which has generally been followed and without change since it was first described in 1911.[2] All of the other 685 patients received only one, preseasonal injection of pollen extract emulsified in Falba and Atreol.[3] The 344 patients treated by traditional methods (and some others not here tabulated, but treated otherwise than by these programs) will be the subjects of separate reports.

The efficacy of emulsified extract,[4] and incidentally its absolute safety when properly prepared and administered, having beyond question been established, the 685 patients were subjected to special scrutiny. From this study, which embraces the largest series of pollen sensitive patients ever given a single type of treatment under identical conditions, we hoped to learn how much extract to give and when to give it.

RESULTS

Although the pollen season of 1958 turned out to be one of the worst on record, the standards set up in the first papers in this series were maintained. Again, any patient who only thought he had suffered any symptoms of any degree or type, however mild or transient, and for whatever reason, but experienced during the pollen season (August 11 to about October 26, 1958) was termed a failure. No patient had to present objective proof of what might sometimes be considered subjective discomfort. Despite the use of this all-embracing definition, only 113 patients would admit to any symptoms, however mild. And of these, not one did not consider himself better off than he had been for the ragweed pollen season of the year before.

Analysis proved that in fifty-six patients, the symptoms coincided with dates on which new, untreated, inadequately or otherwise treated patients were similarly afflicted. All of their symptoms were successfully suppressed by the use of dexamethasone.[5] Discussion of the other fifty-seven patients will, for the moment, be deferred.

RELATIONSHIPS

The single injections were given to 388 males but only to 297 female patients because more males were referred for emulsified extract injections. In many cases their work, involving travel, made weekly injections impractical, or else, in the absence of travel, the hours of their work made weekly injections impossible. For the first group, despite years of difficulty, when in areas of high pollen counts (as for example, Chicago), it was a case of either single injection treatment or none. It was as pleasing as it was unexpected to learn that despite their heavy exposure, those who travelled did better than all of the other patients studied, recording not one failure. These are the most stable patients, and these are the patients afflicted with the fewest (and in many cases, no) other forms of allergy.

TABLE I. THE PATIENT POPULATION GROUPED ACCORDING TO AGE

Years	4	5-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80
Number of patients	1	52	201	118	118	107	54	27	6	1

THE POPULATION TREATED

The first table shows that every age group can be treated. The youngest patient was four and the oldest eighty years of age. Approximately one third (201 of 685) of the number of patients were in the group aged ten to nineteen years. Their parents' motives were compounded of a wish to see that they missed no school and yet had time and were free to enjoy outdoor activities uninterrupted by summertime injections. If we add to these, the patients below the age of ten and also those between twenty and twenty-nine, the total of 372 includes as well, the infants whose parents did not want to subject them to the dangers and inconveniences of weekly injections, and the younger parents who took single injections because they had more important things to do with their time.

The older patients do not like perennial programs of injection treatment because they are forced out of doors during bad weather and frequently, visits to the physician interfere with winter vacations. The many physician patients do not, for themselves, like to take injections. They, having been treated with success, refer the members of their immediate families, their office and laboratory staffs, and their relatives and friends so that they are not, in their turn, bound to the perennial injection program. For whatever reasons (other than their lesser cost) the single injection treatments appear to appeal to every age group.

What of the 344 patients given multiple injections? Almost all have been treated for periods of five to twenty-five years and in many cases take their injections at intervals of six weeks. They are doing well and are being left alone only because there is no good reason for them to

change. But as each has used his year's supply of extract (when injected by a participating physician) and returns for annual re-evaluation studies, he may, if he wishes, choose the single injection type of treatment. A patient may also by simple request and at his own convenience change from the single to the multiple visit program. Of more than 3,000 patients, five have done so.

Some of the patients who do not choose single visit injections usually suffer from many sensitivities, or from more than one disorder. Because they must, in any case, return at regular intervals, they often want to continue with their injections taken every few weeks. This is as good an excuse as any for visiting the physician's office. If closer supervision buttresses their anxieties or makes them in any way feel better, the practice is certainly harmless.

TABLE II.
THE NUMBER OF PATIENTS GROUPED ACCORDING TO DURATION OF DISORDER(S)

Years of duration	1-10	11-20	21-30	31-40	41 or More
Number of patients with bronchial asthma only	80	47	17	5	7
Number of patients with allergic coryza only	145	68	23	14	3
Number of patients with bronchial asthma and allergic coryza*	110	103	37	14	5

*In cases in which both disorders had been present, only the duration of the longer disorder was listed. The number of patients tested does not total 685 because in seven, the disorder was neither bronchial asthma nor allergic coryza.

THE TYPE OF PATIENT TREATED

From the second table, it can be seen that the patients who choose single annual injections are no longer seekers after novelty because the novelty has long since worn off, especially in those who have had ten or more injections of emulsified pollen extract, and, as well, extracts of animal danders, and often of influenza or poliomyelitis or tetanus vaccines. These patients have been sick indeed, and for decades. It would not be fitting to list exactly how many had been subjected to five or more consecutive years of multiple visit treatments with no results whatsoever. The number represents too staggering a condemnation of traditional injection programs.

Of these, almost 200 had never taken any injection treatment at my office or had ever taken any injection treatment at all, because of the disapproval of their physicians or else because of their own aversion to injections given weekly for indefinite periods of time. There are a great many more such patients than is commonly supposed.

More than one fifth (156) of the group suffer from seasonal pollen asthma, and 269 more from both hay fever and asthma. There is nothing subjective about their multiple hospitalizations for ragweed pollen and otherwise caused status asthmaticus.

When both disorders are, or have been present, the hay fever usually preceded the asthma but sometimes accompanied and occasionally followed

it. Although the two types of respiratory pollinosis had often been endured for different lengths of time, only the duration of the longer manifestation of seasonal allergy is tabulated.

Of the 685 patients treated, only 253 suffer from upper respiratory tract pollinosis alone.

The disorders of only 678 patients are listed. The remaining seven suffer from other types of pollen allergy. They represent less than 1 per cent of the number treated. Because none were failures, their inclusion in the tables distorts none of the results.

Although in a typical allergy practice, many of the patients can recall past years of remissions, the group here studied differs in that severe symptoms have been suffered for many successive seasons with no remissions during years of low pollen counts. For approximately half the population (335), the disorder had been present for up to ten years and in 218 more for eleven to twenty years. These are hard, lean, tough, and cynical patients who have never, in the past, been "placebo reactors." They have not changed character.

TABLE III.
PATIENTS GROUPED ACCORDING TO SKIN TEST REACTIVITY

Testing solutions in P.N.U./ml.	P.P.P.	+100	+1000	+2000
Number of patients	109	104	113	359

The above P.P.P. refers to positive responses to pressure puncture (scratch test).

THE SENSITIVITY OF THE PATIENTS TREATED

A glance at the third table shows how often the extremes of sensitivity, as shown by skin test responses, are represented. In the first quartile are the 109 patients so allergic that they respond to scratch or pressure puncture positive tests often to extremely dilute solutions of extract.

To exemplify the type of sensitivity met with, one patient had, for a period of more than forty years, flatly been refused all injection treatment. Because skin tests had previously caused systemic reactions, a pressure puncture test was applied twenty minutes after the subcutaneous injection of 0.3 ml of epinephrine 1:1000 and the ingestion as well of two tablets, each 8 mg, of chlorprophenpyridamine maleate (Chlor-Trimeton, Schering). The resulting response extended around and up the arm. In this same category of sensitivity is a physician's secretary who had suffered thirty separate systemic reactions on her way up to 50 "units" of commercial extract, although at some levels the dose injected was mixed with epinephrine and was repeated as often as five times before an increase of 0.01 ml was attempted. Both of these patients subsequently took 2500 P.N.U./1.0 ml of emulsified extract with no immediate or subsequent ill effects.

In the fourth quartile are included the older patients and those with

bronchial asthma (although not without exception) in whom the skin test response could only be elicited with stronger solutions. But contrary to reports in the literature and my own past wrong opinion, in no patient was it necessary to use a solution stronger than 2000 P.N.U./1.0 ml to elicit wheals, pseudopodia and flares. Transient false positive reactors were ruled out by the repetition of the test in no patient less than twice, and in some patients on ten or more separate occasions. In no patient was there a response to control solutions. No patient who failed to respond to a skin test was ever treated. Conversely no patient was given an injection unless all the other criteria of allergy to ragweed pollen were present and proven.

In every case in which there was any shadow of a doubt, however insubstantial, the patient was given neither type of treatment and told that should there be symptoms during the ensuing pollen season, he would be comforted by drugs alone. These patients have been referred to as having been treated by other means. Some of these did show positive skin test and conjunctival responses during the season. They will return for treatment for the following year.

Approximately one third of the number of patients (217) could be grouped into the middle two quartiles. Theirs is the normal and typical degree of sensitivity seen in an everyday private practice. The 344 patients treated by the multiple injection method almost all fall into these two same categories.

TABLE IV. PATIENTS GROUPED ACCORDING TO CONJUNCTIVAL REACTIVITY

Testing solutions in P.N.U./ml.	+10	+20	+40	+80	+160	+320	+640	+1280	+2560	+5120	+10,240	−10,240*
Number of patients	11	31	50	44	45	40	47	34	34	22	22	279

*These patients were allergic clinically and by skin test, but since they demonstrated no ophthalmic clinical symptoms, showed negative response at the −10,240 P.N.U./ml level.
The number of patients tested does not total 685 because in 26, concomitant allergic and non-allergic ophthalmic disorders would have given equivocal results.

THE CONJUNCTIVAL RESPONSE

In the fourth table the patients are grouped according to degree of conjunctival response. Twenty-six are not included because they, at the time, suffered from concomitant allergic or non-allergic ophthalmic disorders, and tests would not have indicated any degree of sensitivity. Two were blind, both congenitally. In a few children, who were tearful at the prospect of tests, there was no point in forcing the issue. But, positive responses were present in 380 patients and absent in the others (279). By increasing the strength of the testing solutions to 15,000 and 20,000 P.N.U./1.0 ml ophthalmic responses can be elicited in more but not in all patients.

Had any of the 156 asthmatic patients who had never suffered from

ocular symptoms shown a positive conjunctival test, it would mean nothing. In a patient with only nasal, palatal or internal ear symptoms, the presence of a conjunctival response is also a matter of chance. But in clinical practice, there are two valid reasons for doing conjunctival tests, although of the strengths listed every other solution may conveniently and with safety be omitted. First, in no patient who suffered from conjunctival symptoms did the test fail to elicit a response. Second, in every case in which we used the old Falba-Atreol incompletely emulsified but effective injection, the few mild systemic reactions seen occurred only in patients who responded to conjunctival tests and in all cases to solutions weaker than 320 P.N.U./1.0 ml. It should be stressed at this point that the definition of a "systemic reaction" includes any discomfort although limited to mild nasal stenosis, coryza, epiphora, sternutation or the appearance on the skin of just one urtica!

It is for these two reasons that we think ophthalmic tests are worth doing although we do fewer with the passage of time. We can now accurately test the degree of emulsification of our extracts. We do not therefore need the conjunctival response to warn us of the possibility of a systemic reaction. With better emulsification, the doses injected are, for the present, being given to some patients in greater amounts, and to others in lesser, and so few reactions have occurred that they are not worth tabulation. But the decision to do fewer conjunctival tests is not based only on these observations, but on others to be reported upon in much greater detail in a separate communication.

In any case, we have, generally, been able to demonstrate by means of studies done on more than 3000 patients, each given from one to ten or more emulsion injection treatments, that there is no invariable correlation whatsoever between the clinical result and when present, the initial, the subsequent, the seasonal and the post-seasonal conjunctival reactions. As far as we have gone, the patient with the greater conjunctival response has been given the lower dose of emulsified extract. In the present study this was true of forty-three of 139 patients who because of such conjunctival responses to high dilutions of extract were given comparatively small doses, that is, 3500 P.N.U. or less. They reported symptoms which could have been considered as due to the few units injected. But ninety-six others who responded at the same levels of sensitivity and were treated with doses of the same magnitude went through the season with no symptoms at all.

Fifty-six of the patients suffered symptoms which we could prove were caused by exposure to pollen. There were fifty-seven other patients who, during the season, also reported having suffered typical symptoms. We could in each of these prove the symptoms not to be caused by pollen alone. These patients are regarded as failures in treatment because they thought that their symptoms might have been caused by pollen. Only by accepting their statements at face value, could we be sure of some freedom from bias,

if this is at all possible in any study in which the physician is vitally interested.

In some of these patients, the degree of sensitivity as measured by the conjunctival test increased, while in others it decreased, and in a fair proportion there was little or no change. Since in these same patients, the skin test response remained unchanged, there was no good reason to believe that the conjunctival positive response means any more than does a positive reaction to an intracutaneous test, excepting for the fact that in patients who respond conjunctivally, we are measuring the amount of reaction to pollen extract, in an organ actually and directly involved. This does not necessarily parallel the patient's reaction to exposure to actual pollen which represents, when lodged in the eye, a greater dilution of extract.

There has so far not been brought forward any immunological basis for concluding that any response due to reagins should change because of injections of pollen extract, however administered. It is frustrating indeed, to note by the coarse measurements involved in conjunctival and intracutaneous tests, that these responses may be greater than they were before treatment despite the patients having presented a perfect clinical result. One might wish that this were otherwise, but it is not.

TABLE V-a.
GRADATIONS OF DOSES ADMINISTERED TO THE MAJORITY OF THE PATIENTS

Dose in P.N.U.	2500	3000	4000	5000	6000	7500	10,000
Number of patients	80 (29)	41 (10)	18 (4)	106 (27)	27 (2)	170 (24)	213 (12)

TABLE V-b. NUMBER OF PATIENTS TREATED WITH INTERMEDIATE DOSE LEVELS

Dose in P.N.U.	1000	1250	1500	2000	3500	4250	7000	8000	8500
Number of patients	4 (1)	1	2	8 (1)	3 (2)	1	6	4	1

The numbers enclosed in parenthesis denote the patients who, at each dose level, suffered symptoms of any type, caused by ragweed pollen or, during the season, by any other allergen or non-specific irritant.

THE DOSE INJECTED

The fifth table is for convenience given as two tables, labelled V-a and V-b. To repeat, for emphasis, there is no quantitative test which tells us what the ideal dose for any pollen-sensitive patient should be, no matter how the injection of pollen extract is administered. All present programs are therefore truly exploratory. When a patient does not respond adversely to a smaller dose, he receives a greater. It is said that each dose gives a patient such protection that he is able to take the next higher dose. This is an obvious fallacy, and an example of circular thinking. The patient safely took the higher dose and was somehow, therefore, thought to have been prepared to take it by having taken the preceding

smaller dose, because the larger dose was taken with safety. Had the larger dose not have been preceded by a smaller dose, a hypothetical "reaction" might supposedly have occurred. This argument appears to be strengthened by the fact that patients given large doses without the preceding smaller doses have occasionally reacted adversely, either locally or systemically.

But many patients who have taken the smaller doses with no local reaction and without any systemic response do, however also occasionally, react adversely to the larger dose. And also, patients have similarly reacted to the same or a smaller quantity of injected extract. In such cases, we postulate that a back-seepage reaction has occurred, or that when the dose was increased, the increase in quantity was too great. We forget how much this argument is weakened by the fact that many patients do not so react, and, of course, no one knows how the patients would have reacted, had the smaller dose not been given, because in no patient can the procedures be repeated, and under experimental conditions.

Further proof of the exploratory nature of the traditional programs is shown by the contradiction inherent in the standard tables of successive doses recommended. Of a concentration ten times more dilute than that which elicits a positive skin test response, 0.1 ml is injected. A patient who reacts to a 1000 P.N.U./1.0 ml solution or its equivalent would then receive 0.1 ml of a 100 P.N.U./1.0 ml extract. But the skin test represents a quantity which is approximately 0.01 to 0.02 ml, that is, a dose of 10 to 20 units. And 0.1 ml of 100 P.N.U./1.0 ml also represents 10 units. But the patient who receives his first injection on the day of his skin tests has proven himself capable of taking with safety 20 units given intracutaneously, a route from which absorption is quite quick. The total received, then, varies from 20 to 30 P.N.U., and yet the next dose given three to seven days later and subcutaneously, is often 20 P.N.U. or less. I have, in thousands of patients, given a second injection greater than that often administered (but not thought of as an injection) in the form of an intracutaneous "test" and have never met with one adverse reaction, if only because I considered the "test" both as a test and an injection.

Our patients are, therefore, for reasons of convenience, and sometimes caprice, (otherwise elegantly termed randomization) usually treated with a single dose of 2500, 5000, 7500 or 10,000 P.N.U. If, at any dose level between these, as so rarely occurs, there is the slightest indication of a local reaction, although barely palpable, and only by a *tactus eruditus*, it is our present practice to give no more pollen extract then, or later that season. These patients do not suffer subsequent systemic reactions. In the early days of emulsion injection treatment, some patients who presented no such local reaction did occasionally, and within the hour, suffer from mild transient urticaria. But the patients whose treatment ceased at the point of such local reactions clinically did not do any worse

than did the others, proving once again that all dosage schedules including our own are, at present, purely arbitrary.

"Although it is not germane to the present study, it is further of interest to point out that there was no regular correlation in his study between the total amount of pollen extract administered, the duration of treatment, the duration of symptoms and the therapeutic response." This quotation is taken from a paper published in the *Bulletin* of the Johns Hopkins Hospital 69:287-294, 1941. Its authors are Walter L. Winkenwerder, Carl Arbesman, Leslie N. Gay, and Harry Eagle. No comment!

The patients given the four standard dose levels are listed in Table V-a. Those given an intermediate number of protein nitrogen units are listed in Table V-b.

Originally it was planned to place representative or perhaps equal numbers of patients in all the major, and, as well, in the intermediate categories of doses. It became too much of a nuisance to continue, because of the patients given any one of the four major doses listed, all did almost equally well, proving that a patient can do well at any level of dosage if he receives exactly the dose he needs no matter what it is. The fact that good results are seen at all dose levels proves the validity of single injection treatment with emulsified extract because the best dose for a patient to take is the highest dose he can safely tolerate. We cannot, in the present state of our knowledge, insist of it that emulsion injection treatment make possible, as well, a single dose suitable for all patients. But from work in progress it appears that this also may be closer than we realize.

In other words, all of the studies so far done have shown that the first dose, the last dose, the highest, and the grand total number of units are no more than uninspired guesses. To some patients, doses greater than skin and eye test levels suggested had been given, and to some others, less. Since in no case was the difference great, and hardly worth the explanation, an occasional "picker up of unconsidered trifles" has made the most of this apparent major discovery of a minor inconsistency.

As an amusing example, one afternoon all of the available emulsified extract had been used, and all of a new patient's tests suggested a total dose of 10,000 P.N.U. There was, however, on hand, only 0.45 ml, or 4500 P.N.U. of emulsified extract. The patient, who came from a distance, was given this dose. It was brought to the attention of 45,000 physicians, few of whom had read the original paper, that the "glaring inconsistency" somehow invalidated the results.

What the two tables do show is that the 685 patients reached the pollen season with a great deal less variation in dose or magnitude of dose level, than would any comparable groups of patients treated by the multiple visit program, since these latter would include patients given every intermediate dose from 1 unit administered intracutaneously for co-seasonal effects, to 100,000 units injected weekly on a perennial basis.

Of the 685 patients, 569 fitted into the four categories, and the eighty-six others could certainly have been given 0.1 to 0.2 ml more or less, and made to fit into the same categories. The difference would certainly not have been earth-shaking.

What is not obvious is the fact that the patients who routinely reacted systemically to doses of 0.1 to 1.0 P.N.U. in aqueous extract safely took as a first and only dose, 10,000 to 250,000 times the postulated amount of injected extract had it been given in saline and according to the traditional program.

In a paper in preparation will be reported the results of treating another series of patients but with small doses directly related to positive conjunctival responses to extracts in high dilution. Those reactive at the 5, 10 or 20 P.N.U./1.0 ml level received only 500 P.N.U. For each of the successive strengths the dilution eliciting a positive response is followed by the dose placed in parentheses, that is, 40 (1000), 80 (1500), 160 (2000) and 320 P.N.U./1.0 ml (2500 P.N.U.).

If the results to be tabulated prove to be as good as those so far reported upon, then if the reactions possibly due to back seepage or incompletely emulsified extract can be excluded, those postulated as being caused by rapid absorption (relative overdosage) will have been lessened in number although now fewer than 0.001 per cent.

The successful evocation of a systemic reaction by either type of injection has, in our patients, made no difference in the clinical results, some doing well and some less well. This would suggest that systemic reactions differ from anaphylactic shock. In the test animal artificially sensitized, such anaphylactic reactions, when sublethal, are followed by short periods of recalcitrance subsequent to which the degree of sensitivity is the same or else, enhanced.

In three of the patients treated, the injection of acmic doses of emulsified pollen extract was followed (although we cannot be certain of the causal relationship) by ten days of nasal stenosis. They reported no seasonal symptoms of upper respiratory tract pollinosis. But, if we did do it, all we did was to change the dates of their hay fever from autumn to spring.

FIRST MISCELLANEOUS FACTOR

At first glance there is nothing more plausible, and yet, following a second look nothing proves itself to be more ill-founded than the statement that emulsion injections are unsafe.

Well, then, if emulsification is that good, and that safe, why do we not give higher doses to the most sensitive patients, and supposedly better the results? The answer is that they do not need them. It has not been proven that protection is, in all zones of sensitivity a true function of total or ultimate dose. Another answer is that, in our present state of ignorance, it is the better part of wisdom not to push too hard the

delicate proteose-protease equilibrium of these same patients who, often allergic to grass pollen, must take emulsion injection treatment for ragweed pollen sensitivity during the grass pollen season. In those patients who have been protected for grass pollen sensitivity, there is probably less that needs concern us. But, there are many patients whose allergic responses to grass pollen are so minor that although positive responses to grass pollen extract tests are present, they seek treatment only for their ragweed pollen allergy. When they take the injections with the emulsified ragweed pollen extract during June and July, we have no way of knowing exactly how close they may be standing to the edge of having symptoms caused by grass pollen.

This is especially true, because we cannot measure and relate by any simple laboratory tests, the various states of hyperhistaminemia, histaminopexy, the stability of the other enzyme systems known to be involved, and how much may be present and what the functions may be of the sub-sublethal quantities released of 5-hydroxytriptamine, and 5-hydroxytriptaminase, heparin, Slow Reacting Substance A, fibrinolysin, kallikrein, bradykinin, and Bergmann's Cathepsin II, whether as yet measured quantitatively in human subjects. When we can, we will have taken the first small step toward giving exact dose single injections which, even then, will probably be administered in emulsion form.

A mathematical analysis of all injection treatment, including the present, shows that the results reported cannot be placed in a category in which the degree of confidence is at the 95 per cent level. This degree of uncertainty does not invalidate the studies, but it does, when it is realized as being present, force honest investigators to note that "further work is needed before a final conclusion can be drawn." Adding additional numbers of patients will not necessarily add to the validity of such conclusions. On the other hand, we are indebted to an unknown writer who, in London in 1837 said, ". . . Nor could knowledge ever have arrived at its present amazing height, had every intermediate step in the ladder of science from profound ignorance and slavery of intellect been disputed with bigoted incredulity."

To digress further, comment has been made that patients given an over-dose of aqueous extract go into anaphylactic shock, and that the unbelievably few systemic reactions seen in patients treated with emulsified extracts which may, to repeat, originally have contained small amounts of unemulsified extract, have also been anaphylactoid. This is, of course, as noted, utter nonsense. Anaphylactic shock represents a series of sequential events and a group of simultaneously occurring phenomena not directly related to the measurement of the degree of the anaphylactic state. It is not in any one species as such, identical to what we term and describe as anaphylactic shock in another species. These are loose phrases of general convenience, and related only to the reactions seen

following only superficially similar procedures. None are comparable to naturally occurring allergy in humans, in whom we do not inject horse serum or egg white intraperitoneally for purposes of sensitization and after an "incubation period," re-inject a small quantity intravenously for purposes of inducing shock.

If any allergist today thinks that by giving sub-sublethal doses of pollen extract, and that by gradually increasing the amount injected every three to seven days, he is giving the patient "antibodies," and that such antibodies are not only formed, but are "free floating," and then as such, protect the antibodies attached to the "shock organ," as "sessile" antibodies, and that, again, an antigen excess uses up the number of such "free floating antibodies," and that therefore some of the antigen reaches the "shock organ" and causes a reaction, then he believes in something which is completely untrue. It is incredibly difficult partially to desensitize an animal and such lessened sensitivity rarely lasts more than a few days before the original state and degree of sensitivity return. There is not one bit of any type of evidence that this pretty picture occurs in humans. Since 1956, it has represented nothing more than the imagined pot of gold at the end of a rainbow which existed only in a land of dreams.

That allergic patients can be treated successfully by such injections progressively increased in amount does not prove the hypothesis of partial desensitization to possess any basis in fact. All we can truly say is that it has been observed that patients subjected to this crude procedure have apparently been made clinically less response to exposure to pollen. We do not know which injection, if one, was responsible. It may well have been the last and only the last.

It has, however, also been observed that some such patients have been sensitized by being subjected to these same procedures. It is also known that many others have been made neither better nor worse.

For just so long as two physicians of equal stature can state that for the one, 0.001 of a single unit, and for the other, 100,000 units each injected weekly are the doses needed to achieve good results, the obvious conclusions to be drawn are that both are right or that both are wrong or that one or the other suffers from delusions or, else, that both are reporting clinically observed states and that the quantities involved in the procedures are not directly related to the results reported upon unless there is a presently unknown relationship between dose injected and time. And, of course, any procedure which has for fifty years not been changed is, in this day and age, suspect.

There are at present only two valid reasons for giving emulsified extracts. First, they are safer to give and, second, with them there are almost immediately apparent measurable clinical results, usually within three weeks.

TABLE VI.
DISTRIBUTION OF INJECTIONS ACCORDING TO DATE OF ADMINISTRATION

Dates	April	May		June		July		August	
	14-30	1-16	19-30	2-13	16-30	1-16	17-31	1-15	18-29
Number of patients	35	160	208	124	46	49	40	14	9

IDEAL DATE OF INJECTION

According to the sixth table, 627 of the 685 patients were treated during what appears to be the ideal period, that is, between May 1 and the end of July. The convenience of the patients treated at earlier dates was catered to in that, if they reported for injections at such dates, the treatment was given them to save them a second trip to the physician's office. They all cheerfully accepted the fact that they might have difficulties. None objected. Only eight of the thirty-five treated before May 1 reported any symptoms.

The twenty-three patients treated between the dates of August 1 and 29 had not as yet suffered any or more than mild symptoms with exposure to ragweed pollen. Only five of these patients did not respond with a perfect result. The numbers represented by both the "early" and the "late" groups are too small to be amenable to statistical manipulation, but it would appear from purely superficial extrapolation that the results are not as good in patients treated before May 1 and after August 1 as they are in patients treated between these dates. But, for the ragweed pollen season of 1959, these same patients will get injections at what is, at the moment, considered to be the best time, although some may again receive their injections before the first of May and after the first of August. The results achieved in them will be reported upon a year from now.

TABLE VII. DISTRIBUTION OF PATIENTS WITH SYMPTOMS ACCORDING TO DATE SYMPTOMS FIRST OCCURRED

Dates	August		September	
	3-16	17-31	1-13	14-30
Number of patients	17	54	23	18

The number of patients does not total 113 because for 1, no date was reported.

DATES ON WHICH SYMPTOMS OCCURRED

For the seventh table we are short one patient because he was interviewed after the season and could not be pinned down to an exact date on which his transient nasal stenosis became apparent. All of the

seventeen patients who suffered symptoms before August 16 were known to possess other sensitivities, especially to molds and to plantain and grass pollens. These last are seen locally as late as September because of second crops of grasses grown for hay and winter coverage. They are not a major problem and are not noted in pollen surveys. But, in patients who live in the country, they can cause just enough difficulty to make it impossible to place the patients into categories which are neat and tidy. Some of these patients are farmers and, having planted and harvested such second crops of grasses purposely left to grow to maturity with obvious pollenation later in the year than the dates usually given, can pinpoint the cause of their symptoms. These may be due, however, to the cumulative effects of both the grass and ragweed pollens. And, of course, some of the patients known to be allergic to ragweed pollen may suffer as well from sensitivities to other as yet undiscovered seasonal allergens.

Similarly, all of the members of the "late group" were more-than-usually allergic to house dust. In New England, long before the temperature has fallen to 30°-32°, and widespread, long spells of rain have cleared the outside air, the heating systems have been turned on. The house dust, which has been deposited on and behind radiators and in vents during all of the summer months, then goes into the air circulating in the household. The ragweed pollen sensitive patients in this group suffer exacerbations of their symptoms while the pollen count is decreasing outdoors, but on a date when turning on the heat systems exposes them to house dust and, of course, the pollen present indoors as part of such dust.

Almost all of the fifty-six patients whose symptoms could be proven, beyond any doubt whatsoever, to be caused by ragweed pollen alone were grouped in the middle two quartiles. The less obvious but important conclusion which can also be drawn from the seventh table is that the treatment is not, in any sense of the word, non-specific. In every patient a known symptom-causing allergen, for which treatment was not given, caused, as it did before treatment, typical responses following exposure to such an allergen.

TABLE VIII. APPARENT RELATION OF SYMPTOMS TO DOSE LEVEL

Dose in P.N.U.	1000	2000	2500	3000	3500	4000	5000	6000	7500	10,000
Number of patients	1	1	29	10	2	4	27	2	24	13

APPARENT RELATION OF SYMPTOMS TO DOSE

The eighth table is a statistician's nightmare. It will be noted that the first word of the title is "apparent." According to which of the four current schools of statistical theory one belongs, the numbers involved

may be manipulated to result in many conclusions, all equally wrong. The use of statistical methods in the evaluation of the results of treatment with pollen extract will be reported upon elsewhere.

Should we choose 6,000 P.N.U. as a minimum adequate dose the patients should be given, then, only thirty-nine of the 421 patients given this or higher doses suffered any symptoms. But, since we have no right to choose this level, we can take the 5,000 P.N.U. dose as our dividing line. In this case, sixty-six of 685 patients were not adequately treated. But we know that only fifty-six patients in all could be proven to have responded to ragweed pollen alone. Where, then, is the knot that needs unraveling?

The table, in the first place, should never have been made up excepting as an example of how tables should not be set up. All similar tables previously published are equally without foundation. The symptoms are apparently related to dose levels but all such tables omit concomitant relationships. We pretend that in a given area at a given time all of the patients of equal sensitivity are equally exposed. We also pretend that our studies are concerned with numbers of patients so large that mutually contradictory factors will be canceled. The present study concerned with what appears to be a large number of patients does not provide satisfactory proof that the symptoms are indeed related to the level of dose. The symptoms are real. The dose level is, however, based on the crude observation that sensitivity can be measured by the fortuitous responses in the eyes and skins of patients suffering from respiratory tract allergy. But, the skin test, as we know, is rarely changed by the injections. It is always assumed to be a measure of the patient's clinical sensitivity as of the date of testing. We have no method of relating it to the symptoms suffered in the past or presumable to be suffered in the future. In other words, in the treatment of pollinosis we test "backwards" but inject "forwards."

If a positive response to a scratch or an intradermal test tells us what the first "safe" dose should be, how do we explain the fact that when we test the same patient at each subsequent visit the skin test response which has not changed no longer represents the dose to be given since, at each visit, we plan to administer a larger dose? In other words if the skin test response is not changed how can it, at the first visit, tell us what we can safely administer and yet at the second injection or the twenty-second lose this property of imparting information? In fact, should the test response be larger, the dose administered should be smaller. But each test is itself an injection.

The administration of emulsified extract does not resolve the implied contradiction. Should a patient who has taken 10,000 P.N.U. of aqueous extract wish to change to a single, annual injection of emulsified extract, his conjunctival and intracutaneous test responses may indicate a dose of 2,500 P.N.U. But the patient may, with safety, have taken, as of the

previous visit, 10,000 P.N.U. We would certainly not hesitate to give him the same 10,000 P.N.U. this time in emulsified form. Equally without reason, when a patient's tests show that he should take a 10,000 P.N.U. injection and if he, also, at the previous office visit received 10,000 P.N.U. of unemulsified extract in saline, we also give him an injection of 10,000 P.N.U. of emulsified material.

And in both patients we have no method of judging either local differences in exposure or of measuring individual differences of response and degrees of discomfort. The patient in whom such measures prove mild clinical allergy to be present may react to massive exposure and be just as sick as the unprotected patient who is faced with a small quantity of the same pollen. Generally speaking, the patients given the higher doses did better, but these same patients, in any case, do not do poorly. The patients with the lower doses are obviously not as often made symptom-free. But then again it takes little pollen to make them sick.

It is, as a matter of fact, remarkable that, with their degree of sensitivity as measured subjectively by their histories or pseudo-objectively by their tests, all of the patients were pleased with the results. The sickest patient was better than during any previous year on the basis that the hours of symptoms were fewer each day for the same number of days or lasted for the same number of hours each day, but there were fewer days in all.

One of the easiest criteria for judging successful treatment is to count the number of tablets used of any drug the patient requires for symptomatic relief. One example will show how this is not always satisfactory.

A patient in this series first reported that the 1958 season was the worst that she had ever experienced. Her single, annual injection treatment had been preceded by four years of perennial, multiple-visit injections. When a review of her history proved that during the pollen season of 1954 she had taken almost 500 tablets of an antihistaminic agent and that the quantities had decreased by approximately 100 for each successive season, that is, to 400 for 1955, to 300 for 1956 and to 200 for 1957 and that, for 1958 she had been issued 100 tablets and had not used them all, she then recalled the additional activities she had been able to follow during the season of 1958 and cheerfully revised her opinion as to the results of treatment. Of such gossamer is the web of clinical evaluation woven!

Other factors make tables such as the eighth completely unrealistic. One is the booster effect of the second annual injection. A second factor is the probable persistence of protection from aqueous extracts given one or more years antecedently. But almost 200 (196) of the 685 patients had either never before been tested or treated, or had taken no treatment for many years. In the others, although also treated some years previously, the single annual injection may nevertheless have acted to enhance an immune response which was in itself not sufficient to keep the patient symptom-free during the previous pollen season, but yet latent and increased by the injection of emulsified extract.

The results must also be evaluated on the basis that previously untreated patients are known to have limited their activity during the previous pollen season, but as a result of having taken treatment, multiplied their exposure manyfold. An example is that of a boy who spent the previous summer and autumn attending an air-conditioned school. After treatment with the single, annual injection of emulsified ragweed pollen extract, he went to work as a caddy on a golf course. He suffered mild, morning symptoms for all of the days that he worked but, it should be stressed, that he had never at all previously been well enough to work.

Those patients who do poorly one year with a low dose and better a year later with a second injection acting either to boost protection or acting in itself only as a greater dose, may, in the first place, not have had enough. The patient who did not do extremely well for the second season may have received an injection of something good enough to elicit a response by conjunctival or skin testing technique, but not enough of what he needed to protect him against the allergen(s) contained in the whole pollen granule. A separate report will concern a series of such patients treated with another type of extract first used clinically with a mineral oil emulsion more than 20 years ago, and then abandoned for lack of technical knowledge and resurrected for their special treatment. They did poorly but only when the degree of success is measured against the absolute standards of suffering no symptoms whatsoever.

SECOND MISCELLANEOUS FACTOR

By the time the eighth table (now being discussed) appears in print, it will be at least one year out of date. Its numbers can, therefore, only be used for comparative studies by other physicians using similar programs and standard extract. It has been noted that the over-all study made it mandatory for us to inject doses higher and lower than the skin and eye test responses (when the latter were present) would suggest. In other words, no matter what else we learn from the emulsion injection treatment, all studies are motivated by the desire to discover, by whatever means, the ideal dose to be administered in a single injection.

TABLE IX. RELATION OF SYMPTOMS TO DATE OF ADMINISTRATION

Dates	April	May		June		July		August	
	14-30	1-16	19-30	2-13	16-30	1-16	17-31	1-15	18-29
Number of patients	8	22	26	17	9	13	13	3	2

RESULTS NOTED IN PATIENTS TREATED EARLY

Granted some consideration of the variables so far listed, the ninth table would appear to be useful. When it and the sixth table are studied together it is obvious, although the numbers are small, that only three

of the fourteen patients treated during the working days of the first two weeks of August, and only two of the nine treated with reluctance and reservations during the last two weeks of the month had any difficulty. If only we could extrapolate upwards and state that 75 per cent of such patients would do well!

Of the thirty-five treated before April 30, eight needed medicine. It would again appear that the best results are seen in patients treated during the last two weeks in May and during all of June and most of July. But we can only conclude from the table that there are good dates and better dates, but no best or worst dates on which to take injections of emulsified extract.

OTHER MISCELLANEOUS FACTORS

At this point, after studying these tables, the natural question follows, "Is the treatment truly this effective?" Perhaps the author, his co-workers, his colleagues and the thousands of patients so treated are suffering from a mass delusion. Many examples of such delusions can be culled from the history of medicine. Autohemotherapy, for many years, gave as good results as did specific multi-visit courses of treatment. In the early days of multiple visit programs, many critics of the injection treatment with extract for pollinosis made the same criticisms. The fact that the multiple visit type of program has survived does not prove that it also is not a mass delusion. Every physician will admit that the least dependable of foundations for scientific medicine is any patient's own statement. No one has come forward with a study which is not based on patients' opinions and therefore, both types of treatment are equally open to the exact same criticism.

The second obvious question which often arises, as it should, is that of safety. An injection of emulsified "anything" is the safest method of administration we now possess. The procedure is not only safe in the absolute sense but in a comparative one. I would rather give 100,000 injections of emulsified pollen extract blindly and to patients who had never been either previously tested or treated, than give one patient an intravenous injection of ordinary pollen extract, however small, for the proposed measurement of blood trypsin levels. I have never lost my healthy respect for injections of extract prepared in aqueous form no matter how administered.

To repeat what has been said in several previous communications in this series, we always, with extracts prepared in saline, give all patients 0.05 to 0.1 ml of epinephrine (1:1000) added to the extract which is then diluted with normal saline to 1.0 ml or 2.0 ml before injection. Having administered such injections for a period of more than twenty-five years, it is today, in my opinion, the most dangerous procedure to which any human being can be subjected. We have only to place injection treatment with aqueous extracts in another frame of reference to see it in its true

light. It is as though all allergists were engaged in giving injections of penicillin to penicillin-sensitive patients. If there were no available substitute antibiotic agents, that is exactly what we would be doing. And one additional proof of the safety of the procedure is the fact that penicillin can be administered in emulsion form and without reaction. We do, however, have to wait until the patient needs penicillin to prove that we in truth "de-sensitized" him.

When patients are treated with extracts prepared in saline, the allergists must be prepared to meet at any level of dose, unexpected systemic reactions. No one will deny that they so occur and that when they are going to affect the patient, there is no warning. We must therefore not use one standard for the judgment of the systemic reactions so rarely encountered in multiple visit programs and another for those equally so rarely seen with the single annual injection treatment.

To digress again, the studies now being reported upon have been done over a period of almost three decades. They embrace many aspects of the treatment of pollinosis and the results of using a number of methods. The remaining communications concerned with these can only be truly meaningful if each is related to the preceding papers and they to each other. No one communication can list all of the data collected or give all the reasons why it was presented in the form given. Knowledge acquired from studies in progress cannot be permitted to cast its shadow backwards on work done or on papers in preparation, or as is so often true, on papers in press.

One example will suffice. There are at least four physical methods of measuring degrees of emulsification. These are good enough for experiments on animals but they will not do when we wish to treat patients who would react systemically if only given 1 "unit" of dispersed or unemulsified extract. Although I knew better at the time, I described with complete candor the patients treated, however, with extracts emulsified only 99 per cent because that is exactly what they were treated with. We were in the process of proving that we could make better emulsions but we were interested in discovering what the clinical results would be if other physicians used either the incomplete or the partially broken down emulsions at the time available. We could not play leap frog with the earlier studies and publish every other report. By the time this paper appears in print, there will have been administered more than 2000 additional injections of an extract emulsified 99.999 per cent as measured by rigid quantitative biochemical methods.

A fifth method of testing emulsions is that of measuring the skin test response using the emulsion as the scratch test or pressure puncture material. It is accurate but time-consuming. A sixth method uses a dye instead of extract. The amount not coated with oil can easily be separated and measured photolometrically. By these means and others the separate stages of the emulsification cannot only be measured but the stability of

a so-called perfect emulsion with or without an emulsion stabilizer can also be judged as can the differences between different types of emulsifying agents. These will be reported on separately as will the duration of the results seen in the patients purposely treated for only one or two years.

Because the use of epinephrine in emulsified extracts seems so generally to be misunderstood, it must again be said that it is not used as a vasoconstricting agent but as an indicator of the degree of emulsification of the extract. Each 1.0 ml of extract given on the basis of constant volume so that it contains either 2500, 5000 or 10,000 P.N.U. contains 0.1 ml of 1:100 (sic) epinephrine. Patients who receive 7500 P.N.U. are given an injection of 0.75 ml which in their case contains 0.075 ml of epinephrine of the same strength. This injection is obviously equal to 1.0 ml (or 0.75 ml) of epinephrine, 1:1000. We have never observed one patient who, given such an injection, showed any site-of-injection pallor although in these same patients as little as 0.02 ml of epinephrine 1:1000 given in unemulsified form will cause visible evidence of vasoconstriction. None of the patients given emulsified epinephrine with or without pollen extract show any change in respiratory rate, vital capacity, pulse rate, or blood pressure. There is no anxiety and there are no tremors or palpitations. May we from these data with timidity and caution infer that perhaps we have partially succeeded in preparing an extract which is fairly well emulsified?

The question most frequently asked is "Why are patients 'protected'?" First, we provide equal protection to equally sensitive patients given a dose of unemulsified extract. Second, protection was deemed necessary in the early days and before the returns had come in, and while work was in progress to prove the high degree of emulsification obtained. Third, the issue of safety was raised by those who possessing absolutely no background in emulsion chemistry, could only think in terms of the number of units injected and not in terms of the actual effects of the emulsification on such extract. I wrongly anticipated that physicians would, without adequate training, jump to the wrong conclusion that a perfect form of treatment had been discovered. Inexperienced physicians might use extracts not completely emulsified. The first paper therefore, concerned itself not with results noted but with suggestions for the avoidance of possible reactions should anyone, on his own, decide to give such treatment.

This is probably the best place to reply to the "professional viewers of alarm" who have not yet assured themselves that ether is a safe anesthetic, and who have over the years successively gone on record to describe the dire results which would follow the use in allergic patients of epinephrine, ephedrine, aminophyllin, the antihistaminc agents, and the steroid hormones. The older allergists will remember when it was said that when any physician could give an injection of epinephrine to relieve an attack

of bronchial asthma, and also when any patient could learn to inject it into himself, as diabetic patients did insulin, that this was to be the end of the specialty of allergy. No younger physicians would then want to enter a field of so little promise. Some physicians actually left the field, to become lost in the reaches of internal medicine.

It is to be expected that we will always have with us the reactionary conservatives who say that nothing should be changed unless they themselves change it. Any other course quickly inverts their T-waves. And, there will always be the liberal conservative members of the profession who will, year after year, say that "all of us ought to change to the new system and, at the same time, but, not right now."

It is meet and right that every proposed change in a method of treatment which has stood the test of time for fifty years should be looked on with conservative skepticism. There are equally valid reasons for believing, however, that any form of treatment which has not been changed for five decades might be inherently wrong, especially when the first proponents of the method advanced no satisfactory proof that it was anything more than a purely exploratory method of treating allergic disorders due to inhalant allergens.

SUMMARY

Between April 14 and August 29, 1958, 685 patients of both sexes and ranging in age from 4 to 80 years, and suffering from typical ragweed pollinosis, as measured by the most rigid criteria from one year (one patient) to forty or more years' duration (fifteen patients), were treated with a single injection of ragweed pollen extract emulsified in Falba and Atreol. The dose varied from 1000 (four patients) to 10,000 P.N.U. (213 patients).

In only 113 patients were any symptoms of any type, however subjective and no matter how mild or transient, noted. Of these, in only fifty-six could exposure to pollen alone be incriminated. In another fifty-seven, an allergen other than pollen acting alone, or cumulatively with ragweed pollen or other allergens or pollens, resulted in symptoms which occurred during the period of ragweed pollenation, that is, between August 11 to about October 26, 1958. The date for the termination of the season is not exactly known, because these and other patients were referred from a wide geographical area.

The symptoms observed occurred in patients who, by intracutaneous and conjunctival tests, had responded with wheals, pseudopodia, and flares, to four different test levels. They were treated with doses which were based on the arbitrary assumption that the tests indicated the amount of pollen extract to be injected. Although the numbers treated are not sufficiently large to permit statistical validation, it appears that in the thirty-five patients treated before May 1, and in the twenty-three others who took their injections after August 1, symptoms were noted with greater fre-

quency. But, no matter when the injection was given, the patients who received smaller doses apparently did not do as well as did the others. This may be a result of the small dose injected, or else due to the fact that it takes less exposure to pollen for such patients to respond with symptoms. For the following year, some such patients will receive the same dose (booster principle), some higher doses (higher dose—higher protection principle), and some, a less denaturalized pollen extract (incomplete protection principle).

The patients who reported for treatment after August 1 could not have been treated at any other time, but for 1959 will be given injections on dates earlier in the year. The patients treated before May 1 will be given their injections at a later date. The patients allergic to other pollens will be given protection for both.

All patients, presenting symptoms (without exception), did better than they had done for the previous year, which was one of lesser pollenation. But, in 113 patients, some symptoms, whether mild or subjective, were noted, which, in fifty-six, were treated with dexamethasone, and in some of the others with mild antihistaminic agents taken as needed.

In the other 572 patients treated by means of a single injection of emulsified extract, there were no symptoms whatsoever. From the results seen, it can tentatively be concluded that emulsion injection treatment as previously described and here and elsewhere corroborated, represents a major break-through in the treatment of human pollinosis.

REFERENCES

1. Brown, E. A.: The treatment of pollinosis by means of a single annual injection of emulsified extract. V. Ann. Allergy, 17:34-49 (Jan.-Feb.) 1959.
2. Freeman, John: Further observations on the treatment of hay fever by hypodermic inoculation of pollen vaccine. Lancet, 2:814, 1911.
3. Loveless, M. H.: Repository injection in pollen allergy. J. Immunol., 79:68 (July) 1957.
4. Brown, E. A.: Treatment of grass pollinosis with a single annual injection of emulsified extract. IV. Ann. Allergy, 16:510-520 (Sept.-Oct.) 1958.
5. Brown, E. A.: The suppression of the supervenient symptoms of ragweed pollinosis with dexamethasone. Antibiotic Med. & Clin. Therapy (in press).

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THE LAW OF NATURE

"He recognizes that the so-called law of nature is but a simple *résumé*, a brief description of a wide range of his own perceptions and that the harmony between his perceptive and reasoning faculties is not incapable of being traced to its origin. Natural law appears to him an intellectual product of man, and not a routine inherent in "dead matter." The progress of science is thus reduced to a more and more complete analysis of the perceptive faculty—an analysis which unconsciously and not unnaturally, if illogically, we too often treat as an analysis of something beyond sense-impression. Thus both the material and the laws of science are inherent in ourselves rather than in an outside world."—PEARSON, *Grammar of Science.*

STUDIES ON ALLERGENIC EXTRACTS

I. A New Method for the Preparation of Mold Extracts Using a Synthetic Medium

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MOLDS and their by-products are recognized as important causative agents in producing symptoms in patients with contact and inhalant allergies.[1] For the proper evaluation of such patients it is important that the diagnostic and therapeutic antigens be potent, specific and be prepared in such manner as to be free from nonspecific and irritating materials.

In choosing a medium for the growth of pure cultures of molds, care must be taken to exclude ingredients which in themselves or their metabolites are allergenic. It is also important to consider that certain nutrient ingredients may be absorbed onto the mold growth and require such thorough washing procedures prior to extraction as to diminish the allergenicity of the mold extract. These considerations severely limit the use of the usual nutrients which promote profuse culture growth of molds, and have led to the use of various inorganic salts as a "synthetic medium."[2,7] In selecting the ingredients for a medium to give adequate mold growth and to avoid the disadvantages discussed above, the following requirements need consideration:

1. *Carbohydrate Source.*—Sucrose is a sugar which is chemically pure and ash free.

2. *Nitrogen Source.*—(a) Ammonium Sulfate provides Nitrogen and Sulphur. (b) Ammonium Nitrate provides Nitrogen as an Ammonium Salt and Nitrogen in the Nitrate form. (c) Ammonium Citrate provides Ammonium Nitrogen, Carbon, and aids in buffering. (d) Ammonium Phosphate provides Ammonium Nitrogen, Phosphorus as a Phosphate, and aids in buffering.

3. *Sodium Source.*—Sodium Citrate provides Sodium, Carbon and aids in buffering.

4. *Phosphorous Source.*—(a) Potassium Phosphate (monobasic). (b) Potassium Phosphate (dibasic). (c) Ammonium Phosphate. (d) Potassium Phosphate (monobasic) and Potassium Phosphate (dibasic) together act as a buffer system, as well as providing the needed phosphorus.

5. *Carbon Source.*—The carbon available for mold growth in the sugar used is often insufficient to give copious growth, and therefore the use of Citric Acid and Citric Salts is recommended. This furnishes a source for carbon and aids in buffering.

6. *Potassium Source.*—Potassium Citrate provides an additional source of carbon, as well as the Potassium.

7. *Magnesium Source.*—Magnesium Sulfate.

8. *Calcium Source.*—Calcium Carbonate. An excess will serve as a means of neutralizing acid produced during the mold growth and provide more calcium as the salt goes into solution.

9. *Trace Elements Source.*—Research in mold growth has shown that the presence

of trace amounts of certain elements are necessary for some of the enzyme systems, primarily respiratory, and their inclusion in the medium will promote and enhance the growth. For this purpose a mixture of Copper, Manganese, Zinc, Iron and Chromium salts is used.

With the above factors in mind, we have successfully employed a nutrient medium of the following composition, in which the cultivation of a wide variety of pure cultures of molds has been accomplished:

SUGGESTED FORMULA

Center Mold Medium No. 1

Sucrose	40 gm
Ammonium Sulfate	2.0 gm
Ammonium Nitrate	1.3 gm
Ammonium Citrate	1.0 gm
Sodium Citrate	2.0 gm
Potassium Phosphate, Monobasic	0.15 gm
Potassium Phosphate, Dibasic	0.15 gm
Ammonium Phosphate, Dibasic	0.20 gm
Citric Acid	1.0 gm
Potassium Citrate	0.40 gm
Magnesium Sulfate	0.25 gm
Calcium Carbonate	0.8 gm
Trace Elements Stock Solution*	1.0 cc
Distilled Water—q.s.	1,000 cc

**Formula for Trace Elements Stock Solution*

Copper Sulfate	5.0 gm
Manganese Sulfate	5.0 gm
Potassium Dichromate	2.0 gm
Zinc Sulphate	5.0 gm
Ferric Sulfate	1.0 gm
Distilled Water—q.s.	1,000 cc

PREPARATION OF MEDIUM

The ingredients are added to distilled water and allowed to boil gently for one-half to one minute and clarified by paper filtration. The medium is dispensed in suitable containers and autoclaved at 118° Centigrade (12 pounds pressure) for fifteen minutes. The pH of the sterilized solution should be 6.5 to 7.0. Overheating during sterilization should be avoided, because it will result in discoloration caused by the destruction of some of the sugar and thereby render the medium unsuitable for use. A solid conservation medium can be prepared by the addition of 1.5 per cent agar to the above formula.

GROWTH AND EXTRACTION

The sterile medium is inoculated with a pure culture and is incubated at 25-28° C. Depending on the organism, a heavy mat usually develops within seven to fourteen days after inoculation.

The mold extracts are prepared from the entire growth (mat and mother liquor). The fully grown mold mat and culture substrate are homogenized in a Waring Blender and allowed to extract at approximately 5° C for 48 hours. The homogenate is filtered.

The filtrate is dialyzed against distilled water to remove the unused salts

and any other dialyzable ingredients contained in the homogenate. To the dialyzed extract are added the following buffers and preservative:

Sodium Chloride	0.5 per cent
Sodium Phosphate, Dibasic	0.14 per cent
Potassium Phosphate, Monobasic	0.036 per cent
Phenol	0.4 per cent

The pH of the final solution is determined and adjusted to 6.5 to 7.0. The solution is filtered aseptically, tested for sterility and safety, and stored under refrigeration.

To prepare extracts containing 50 per cent glycerine, a volume of glycerine equal to the volume of the dialyzed extracts is added prior to the addition of the buffering salts. The solution is then filtered aseptically and tested for sterility and safety.

CONCENTRATION OF EXTRACTS

Many mold extracts have a low titer of potency and may need concentration. This can be accomplished by means of low temperature vacuum distillation prior to the addition of buffers and preservative.

STANDARDIZATION OF EXTRACTS

1. *Biological Assay.*—Skin tests with serial dilutions of the final extracts are performed on patients with known mold sensitivity, starting with one to 100,000 dilution and working upward to the concentrate in decimal increments.

2. *Weight/Volume.*—After paper filtration of the homogenate, the filtered residue is acetone dried and weighed. The volume of the filtrate is measured. The percentage concentration is then calculated.

3. *Protein Nitrogen.*—Standardization based on a Protein Nitrogen content can be accomplished by use of Phosphotungstic Acid precipitation and determination of the nitrogen content by means of the Micro-Kjeldahl technique.[8]

Since 1953, the following molds have been routinely cultivated and used in the preparation of allergenic extracts; the species successfully grown were those which were recovered by air sampling:

Alternaria	Stemphylium	Fusarium	Monilia
Hormodendrum	Botrytis	Trichoderma	(asexual phase
Penicillium	Phoma	Chaetomium	of Neurospora)
Aspergillus	Acrothecium	Spondylocladium	Curvularia
Pullularia	Nigrospora	Mucor	Macrosporium
Epicoccum	Helminthosporium	Rhizopus	

During this period, all of the above mold species grew adequately with luxuriant spore formation and yielded extracts of clinical diagnostic reliability.

COMPARATIVE CLINICAL STUDIES

Extracts of eight molds were prepared by two different methods: (1) the use of Center Mold Medium No. 1 and the technique described above, and (2) the use of Czapek's Medium, as follows:

FORMULA FOR CZAPEK'S MEDIUM

Sucrose	30	gm
Sodium Nitrate	2.0	gm
Dibasic Potassium Phosphate	1.0	gm
Magnesium Sulfate	0.5	gm
Potassium Chloride	0.5	gm
Ferrous Sulfate	0.01	gm
Water	1,000	cc

PREPARATION OF CZAPEK'S MEDIUM

The ingredients are added to distilled water and allowed to boil gently for one-half to one minute and clarified by paper filtration. The medium is dispensed in suitable containers and autoclaved at 118° C (12 pounds pressure) for fifteen minutes. The pH of the sterilized solution should be 6.5 to 7.0. Overheating during sterilization should be avoided since it will result in discoloration caused by destruction of some of the sugars, thereby rendering the medium unsuitable for use.

The sterile Czapek's medium was inoculated with pure cultures and incubated at 25-28° C until optimum growth was obtained. This usually required four to six weeks. After the development of a heavy mat, the mat was removed from the culture medium, dried between sheets of filter paper, and desiccated. The desiccated mat was extracted with buffered saline on a W/V basis (1:50). Extraction was allowed to take place for 48 hours at 5° C.

The extract was paper filtered, and the filtrate was dialyzed against buffered saline. The pH of the final solution was determined and adjusted to 6.5 to 7.0. The solution was filtered aseptically, tested for sterility and safety, and stored under refrigeration.

The sterile extracts prepared by both methods were standardized on a W/V basis (1:100, 1:1,000, 1:10,000). One hundred patients clinically sensitive to molds were skin tested with extracts prepared by both methods, with the following results noted in the accompanying table:

Molds	Extracts Prepared with Czapek's Medium % Positive Reactions	Extracts Prepared with Center Mold Medium No. 1 % Positive Reactions
Alternaria	29	35
Hormodendrum	17	26
Phoma	17	22
Pullularia	9	22
Penicillium	11	18
Aspergillus	7	14
Helminthosporium	10	13
Fusarium	15	10

These patients were tested by the bio-assay method, using serial dilutions. Only 3-plus and 4-plus reactions were considered positive. Control tests were performed on all patients, with sterile culture medium processed in the same manner as the extracts, and also used in serial dilutions, with negative results. As a further control, tests with house dust extracts in

serial dilutions were also done. The house dust tests resulted in a 37 per cent positive response.

Using the serial dilution method of testing, no constitutional reactions occurred, although severe local reactions were occasionally encountered, more with Center Mold Medium No. 1 extracts than with extracts prepared with the use of Czapek's medium. With extracts prepared by Center Mold Medium No. 1 and the method described, all reactions were immediate; no delayed reactions occurred.

Correlation between tests and exposure was established by means of house dust cultures and mold plates surveys. Skin tests performed with extracts prepared by the use of Center Mold Medium No. 1 were clinically more significant than the tests performed with the extracts made with Czapek's medium, since they presented a greater degree of correlation with the molds isolated from the house dust and culture plates.

SUMMARY

1. A synthetic medium for mold cultivation which adequately supports growth of allergenically significant molds is given.

2. The medium and method presented eliminates nonspecific, allergenic and other interfering factors which may be present in other commonly-used media.

3. A method for extraction, concentration and standardization of allergenic extracts of molds is given.

4. By use of this method the allergenic nature of the mold is at no time subject to denaturing influences.

5. Clinical studies indicate a high degree of specificity of extracts as determined by skin testing, and confirmed by environmental studies.

REFERENCES

1. Christenson, C. M., and Swaebly, M. A.: A manual of clinical allergy. *In* Sheldon, Loval and Mathews (Ed.): Aero Allergens. Ch. 16. p. 293. Philadelphia: W. B. Saunders Company, 1953.
2. Greene, H. C., and Fred, E. B.: Maintenance of vigorous mold stock cultures. Indust. Eng. Chem., 26:1927, 1934.
3. Henrici, A. T.: Molds, Yeasts and Actinomycetes. Chap. III, p. 49-79. New York: John Wiley & Sons, 1948.
4. Levine, M., and Schoenlein, H. W.: A Compilation of Culture Media for the Cultivation of Micro-organisms. Baltimore: Williams and Wilkins, 1930.
5. Mrak, E. M., Phaff, H. J., and Douglass, J. C.: A sporulation stock medium for yeasts and other fungi. Science, 96:432, 1942.
6. Steinberg, R. A.: Growth of fungi in synthetic nutrient solutions. Botan. Rev., 5:327, 1939.
7. Swaebly, M. A., Christensen, C. M., and Grahek, T. A.: Tests of different media for collection and identification of air-borne saprophytic fungi. J. Allergy, 21:404, 1950.
8. Cooke, R. A., and Stull, A.: The preparation and standardization of pollen extracts for the treatment of hay fever. Ann. Allergy, 4:87, 1933.
9. Schaffer, N.: Instructional Course, 13th Annual Congress of the American College of Allergists, Chicago, Illinois, 1957.

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DEXAMETHASONE IN ALLERGY

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SINCE the introduction of cortisone ten years ago, the use of adrenal corticoids in the treatment of allergic disorders has become firmly established. The search for newer corticoids with increased therapeutic effectiveness and lessened side effects has been unceasing. The pharmaceutical industry is to be complimented on its enormous investment in research to develop new compounds and to increase basic knowledge. At this time, it is apparent that there are significant differences among the corticoid preparations presently available. For best results in therapy of allergy, the physician should be aware of these differences.

Dexamethasone* is the generic name of 9 alpha fluoro, 16 alpha methyl, delta-1 hydrocortisone. Its structural formula is shown in Figure 1.

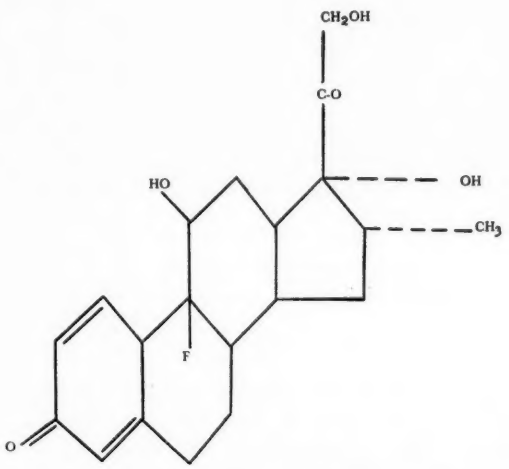

Fig. 1. Structural formula of dexamethasone.

When subjected to animal screening procedures, dexamethasone was of interest because of its extreme potency in inhibiting granuloma formation and a ten-fold disparity between the potency of the compound in the granuloma test and the liver glycogen test. This suggested that perhaps the anti-inflammatory properties of an adrenal corticoid might be separated

*Supplied as "Decadron" by Dr. Nicholas Capeci of the Merck Sharp and Dohme Research Laboratories.

quantitatively from other glucocorticoid activities. The present study was undertaken in an attempt to evaluate the usefulness of dexamethasone in the treatment of allergic disorders.

TABLE I. RESULTS OF THERAPY WITH DEXAMETHASONE
(240 Patients)

Disorder	Satisfactory Results	Unsatisfactory Results
Seasonal hay fever	46	4
Perennial allergic rhinitis	29	13
Allergic conjunctivitis	5	0
Bronchial asthma	103	20
Atopic eczema	6	0
Contact dermatitis	2	0
Drug reactions	5	1
Periarteritis nodosa	2	0
Urticaria	3	1
Totals	201	39

PROCEDURE

Dexamethasone was administered to 240 ambulatory patients suffering from the various allergic disorders listed in Table I. These patients were all observed personally by the authors. The patients ranged in age from two to seventy years. The duration of treatment with dexamethasone varied from five days to seven months.

TABLE II. STEROID COMPARISON
Average daily maintenance dosage of dexamethasone vs. other steroids

Steroid	Number of Patients	Dosage
Prednisone or prednisolone	19	11.6 mg
Methyl prednisolone	10	11.2 mg
Triamcinolone	6	9.3 mg
Dexamethasone	24	1.3 mg

Following treatment with dexamethasone, the patients were classified arbitrarily as having had a satisfactory or unsatisfactory result. Therapy was judged to have been satisfactory if both the patient and the physician agreed that the control of signs and symptoms outweighed any undesirable effects which may have occurred. Although objective measurements such as pulmonary function tests and comparative Kodacrome photographs with a Coreco camera were performed, these were not tabulated individually but were included in the over-all evaluation of the therapeutic result.

Most of the patients had already received other steroids and some were on a maintenance dosage. These were shifted to dexamethasone for comparison. Some patients were started on dexamethosone *de novo* and then shifted to other steroids. Only those patients were given adrenal steroids who had failed to respond adequately to standard anti-allergic treatment.

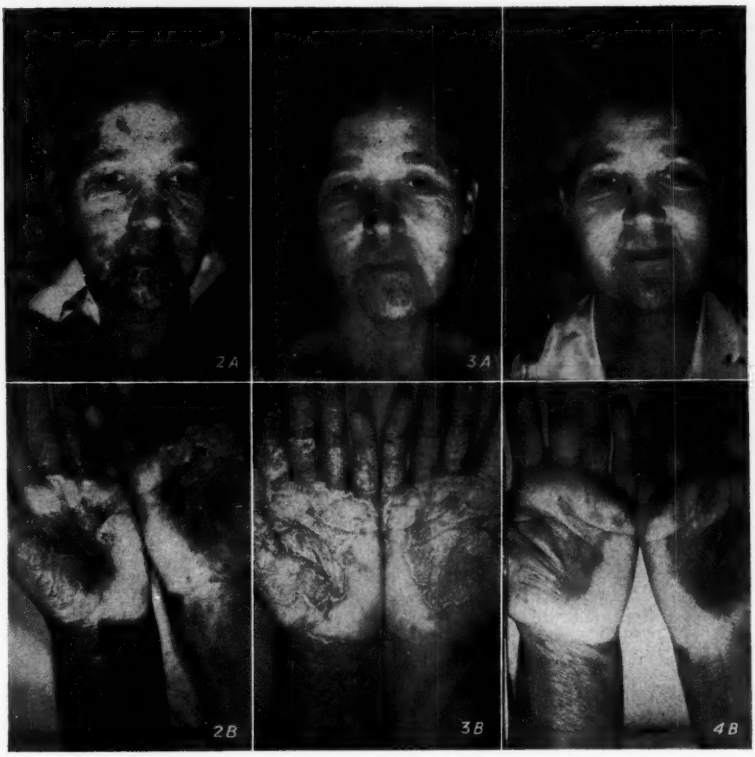

Fig. 2 (a and b). Patient with contact dermatitis before therapy with dexamethasone.

Fig. 3. (a and b). Same patient on fourth day of therapy.

Fig. 4 (a and b). Same patient on fourteenth day, dexamethasone having been discontinued on the seventh day.

RESULTS

The results of therapy are shown in Table I. Dexamethasone was considered a satisfactory therapeutic agent by both physicians and patients in 201 of 240 cases. In our hands, dexamethasone compared well with other steroids.

The most striking finding was increased potency. This is shown in Table II. Milligram for milligram there is no question that dexamethasone is the most potent steroid available. The relationship of dosage to other steroids is shown.

The hormonal side effects proved most interesting. Table III indicates that dexamethasone has somewhat different side effects than other steroids. During the seven months' observation, no serious side effects such as peptic ulcer, osteoporosis, psychosis or thrombophlebitis were noted. Ner-

vousness was fairly prominent. There was a definite stimulatory effect in some patients. The gastrointestinal distress consisted mostly of bloating, belching and mild abdominal pain. It did not appear to be associated with peptic ulcer. Eight of the seventeen patients who complained of gastro-

TABLE III. SIDE EFFECTS IN 240 PATIENTS*

None	168
Increased Appetite with Weight Gain	26
Nervousness	23
Moon Facies	18
Gastrointestinal Distress	17
Insomnia	12
Fatigue	5
Depressed	5
Muscle Pain	5
Edema	1
Headache	3

*More than one side effect in some patients.

intestinal symptoms were examined roentgenologically. The gastrointestinal series was normal in every instance. Often there was an increase in appetite associated with the distress. This occasionally resulted in significant weight gain; but edema occurred in only one patient. This patient had congenital renal glycosuria. Edema had previously occurred on a low-salt diet while receiving hydrocortisone, prednisolone, methylprednisolone or corticotropin. The edema was relieved when the patient was shifted from dexamethasone to triamcinolone. Lack of serious disturbance of the carbohydrate metabolism was noted in two diabetic patients with asthma who were treated with dexamethasone. On small maintainance doses (1.0 mg daily) there was no appreciable effect on the carbohydrate metabolism as judged by the urine sugar or the insulin requirements. The initial effect of suppressive doses could not be estimated because at such times the patients were infected and already out of balance. Metabolic balance studies were not performed.

We did not observe any overt signs of adrenal insufficiency following cessation of therapy. This is not surprising in view of the recent demonstration by Friedman[2] that blood 17-OH steroid levels and corticotropin response tests return to normal within a week after stopping short-term treatment with dexamethasone.

DISCUSSION

Dexamethasone is a very potent agent in the treatment of allergic disorders. In our hands, its potency relative to other steroids is slightly higher against allergic disease than has been reported by others in the treatment of arthritis.[3,4] The order of magnitude, however, is the same. Since dexamethasone is presently available in 0.75 mg and 0.5 mg tablets, this is most satisfactory. These would compare favorably with the 25 mg tablets of cortisone, the 20 mg tablets of hydrocortisone, the 5 mg tablets of prednisone or prednisolone and the 4 mg tablets of methylprednisolone and triamcinolone. It should be emphasized that there is a considerable range of relative potency from one patient to the next.

It is of interest that prednisolone and dexamethasone have the same biologic half time[4] even though, in our hands, the latter compound is nine times more potent.

Undesirable hormonal side effects of adrenocortical therapy appear to vary from one drug to another and from patient to patient with the same drug. Dexamethasone, for example, appears to have stimulating effects on the central nervous system and the appetite (Table III). This is in direct contradistinction to the effects of triamcinolone which has a depressant effect. Knowledge of these differences among the steroids is helpful in choosing the most suitable preparation for the patient.

CONCLUSIONS

1. Dexamethasone was given to 240 patients suffering from allergic disorders. In 201, therapy was judged successful.
2. Dexamethasone is the most potent available steroid yet available.
3. Of 240 patients, 168 had no side effects.
4. Treatment was not complicated by serious side effects such as peptic ulcer, psychosis, hypertension, diabetes or osteoporosis during seven months of observation.
5. The most commonly observed side effects were mental stimulation, increased appetite and epigastric distress.

REFERENCES

1. Arth, G. E., Fried, J., Johnston, D. B. R., Hoff, D. R., Sarett, L. H., Silber, R. H., Stoerk, H. C., and Winter, C. A.: 16-methylated steroids. II. 16 alpha-methyl analogs of cortisone, a new group of anti-inflammatory steroids. 9 alpha-halo derivatives. J. Am. Chem. Soc., 80:3161, 1958.
2. Friedman, H.: Personal communication.
3. Boland, E. W.: 16 alpha-methyl corticosteroids—a new series of anti-inflammatory compounds: Clinical appraisal of their antirheumatic potencies. California Med., 88:417, 1958.
4. Bunim, J. J., Black, R. L., Lutwak, L., Peterson, R. E., and Whedon, G. D.: Studies on dexamethasone, a new synthetic steroid in rheumatoid arthritis—a preliminary report. Arth. & Rheumat., 4:313, 1958.

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Submitted February 19, 1959

THE MATHEMATICAL STATISTICIAN

It cannot be too clearly understood that the mathematical statistician has no such secret wells of wisdom to draw from, and that his science does not justify his going one step beyond the purely numerical statement that—as computed by him from the data he has selected as suitable for his purposes—the probabilities in favour of chance are such and such. There need, therefore, be no hesitation in saying that when the mathematical statistician makes free with the terms *significant* and *non-significant*, he is simply taking upon himself a function to which he can lay no claim in his capacity as a mathematician.—SIR ALMROTH WRIGHT.

ALLERGY IN AUSTRALIA

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IN the Royal Melbourne Hospital there is a large general allergy clinic. It is presided over by Dr. R. H. O. Donald who is an otolaryngologist. In this city there are only a few general allergists in the sense that we know them. To my knowledge very few otolaryngologists have an interest in allergy or allergic problems. If removal of polypi, internal medication, local applications, chemical or electrical cauterizations, and corrections of anatomical defects do not give the expected relief of local allergic symptoms, then they are referred to allergists, and many to the above-mentioned group in the Royal Melbourne Hospital. They have several technicians and follow about the same definite plans that we do in working up a case. After taking a careful histroy, including a rather careful allergic history of present and past symptoms, investigations of precipitating factors, family history, history of operations, et cetera, a general physical examination and a complete ear, nose and throat examination is made including x-rays of sinuses and chest. Then the patient is turned over to the allergy laboratory technicians who make both scratch and intradermal tests as indicated by the consultants, and they make up many extracts. They work toward maximal doses and the extracts used for desensitization are ordinarily mixed so that a mixed bottle sent out for use by the referring physician may have as many as four or five different extracts in them.

I was quite surprised to find that in this laboratory and hospital all the workers belong to certain unions. This led me to think of and make comparisons between the high state of unionization in Australia and New Zealand as compared to ours here in America. New Zealand has a sweeping welfare state which has grown in an amazing way. Much of the socialist program introduced in the U.S.A. since Franklin Roosevelt's time was hastily adopted from New Zealand's. Nearly every one of the salaried people in Australia and New Zealand belongs to certain types of unions. Probably no other country has the proportion of organized workers in the labor force as Australia. Two-thirds of this country's wage and salary force of two and seven-tenths million people, or about one and eight-tenths million people belong to unions. To have a similar proportional strength in the United States, union membership would have to run about forty-six million people. At present there are eighteen and a half million American workers that are union members. The political activity of the unions is such that their political party controls the governments of three of Australia's six states. Union leaders are extremely active in political circles;

in fact, regulatory power of state governments in all phases of activity is so governed.

In a fairly nice hotel the waitress calmly brought two strangers to our table and seated them in the two empty chairs. We were thus introduced to the quaint Australian restaurant custom of filling the tables in use before seating anyone at an empty table; this is the way the waitresses want it. One explained, "It is easier for us to wait on people this way."

At a Unions Federation Council in Melbourne, the union secretary complained that "many hotel keepers give more consideration to customers and guests than they do to employees." In the "pubs" during the slack hours, they put up signs, "This section closed," and the patrons are expected to line up directly in front of the bartender so that he doesn't have to do any walking. He knows that if any argument with his employers arises over this he will be backed up in his union demands. In Sydney, the janitors in the city schools are requesting what they called a "chillblain allowance" through their union. This was to amount to seventy cents a day increase in pay when the temperature dropped below twenty-five degrees.

COLLECTIVE BARGAINING

In spite of the fact that there are unions for almost everyone from nearly all work activities from government officers to police and firemen, from sheep herders up to all bank employes except bank presidents, they have not developed the finesse of arbitration in labor disputes as we have. Every labor dispute that can't be rather quickly settled is arbitrated by an aribtration court in each state. Their results, conclusions and regulations are accepted, court awards are final and they have penal provisions. In South Australia, the maximum penalty for disobeying such a court award is five hundred pounds, over a thousand dollars, or three months in prison. The right to strike is not entirely eliminated but it is hedged with restrictions so that labor leaders complain bitterly that they have no very good weapon against employers. Since government award commissions settle the disputes, the position of labor unions in reference to their importance to membership as it is here, is considerably lessened. The basic wage is around thirty dollars a week and then there are some incentives granted for special skills. For instance, a boilermaker has added to this basic wage of $29.45 in Sydney, a margin of $8.37. A baker has a margin of $10.61; a linotype operator a margin of $10.83. It is, of course, difficult to make comparisons in wages, for the costs of living are very much different in Australia than here. I only knew of one plant in Australia that operated on an incentive profit-sharing program and that is a branch of the Lincoln Electric, which operates under the same plan that they do in Cleveland, paying from 30 to 70 per cent more than the basic wage scales, but their production is higher, about three and one-half times that of an employe in comparable industry. So one hears that some Australians are beginning

to feel that, since they have had in the past few years more of a stake in general world economy and competitive world economy, their efficiencies must be increased. They have tried to protect their market and promote their own manufacturing, but that, too, is causing them headaches, for they are a raw material exporting nation. They must export their wool and minerals and if they aren't traded for manufactured goods, they can't be sold.

In New Zealand we found that the people live oblivious to the cares that beset their American counterparts. The New Zealander gets free medical and dental care, free medicine, a 5 per cent bonus if he saves his money to build a house, many family benefits and the likelihood of a college scholarship for his children. He pays 7½ per cent into the social security program and from 15 to 60 per cent into income taxes. The cost of living is considerably lower than it is here and the standard is lower. The average worker earns about thirty-five dollars per week while a bank president will draw only two or three times as much. The cradle to the grave, welfare state, is well establishd in New Zealand.

A sign in a store "Be Kind to Our Staff, They are Harder to Get Than Customers" illustrates the public attitude and frequently found are a lethargy and a reliance on a government that has tried to equalize every man's paycheck and social posture. In the country store on the South Island a sign was displayed that read "9:30 to 12:30 pm and from 1:30 pm to 5:30 pm—Please observe these hours if you wish to trade here." This is quite a contrast to the same type of neighborhood store that we have in this country where the owner lives in the back of the store and is available after hours especially when the larger chain stores and others are closed. The business controls are such that competition is lowered. A business man from Wellington remarked that he in his cleaning and dyeing business could regulate his offices exactly with his competition and so they had cut down their hours in business so that all would have plenty of time for recreation. I suggested that perhaps they could produce and earn more if they increased their efficiency and work time. His remark was that it wasn't necessary for they had a guaranteed cost and practically a guaranteed income; restrictions prohibited competition and so these controls put the competition in a straightjacket. In the last twelve years the number of people tapping the social welfare till rose from one in ten to one in every two persons in the country. The government economists reason that a welfare state does encourage expansion. It rations credit through controls and the monetary controls regulate the bank, import licenses regulate what produces can come into the country. They reason that high taxes are a disincentive to expand but spreading income broadens markets and increases sales and during an inflationary trend, which accompanies the welfare state, it provides steadily rising prices and so inflation and broadened markets outbalance the high tax disincentive.

Farmers are an exception; there is no export bounty and his products are on the world market. He must produce good meat, wool, butter and cheese economically and he does. He practices modern techniques, fertilizes by air, does scientific breeding and feeding but even he has a support price from government under his prices.

One New Zealander said, "We have grown up under this welfare state; most of us don't know anything else, so we accept it as our way of life, but to an American it is a way of life that would seem to discourage an inspired thought, a spirited day's work or will to do something, anything a little better."

EDITOR'S NOTE: The late Dr. Hugh Kuhn planned to give the above informal talk at the Fourteenth Annual Congress of The American College of Allergists in Atlantic City, New Jersey, on April 25, 1958. It was not prepared for purposes of publication, and is therefore published as a tribute to him, exactly as he wrote it.

NORMALITY AND DISEASE

The concept of the normal is an illusion of our own making. It is not easy to abandon one's illusions. Those who walk among the sick ask themselves many times a day, is this normal or abnormal? The physician who would prevent rather than cure disease must carry the question into that no-man's land where disease is nascent and difficultly discoverable—where does the normal end and disease begin? We are engaged in an issue between life and death and we cannot define our enemy—what is disease? Is it not normal for some men to be infected with non-pathogenic pneumococci—do we not call it abnormal only when the organism is pathogenic? But do we gain anything thereby? What does it aid us to define pneumonia as abnormal when we are not embarrassed to think that a pneumococcus is a normal organism that follows a normal course of reproduction in somebody's alveoli, to the victim's inevitable distress and until he dies—unless treated with sulfanilamide—all in accordance with laws apparently as unchanging as Plato's universals, the whole a normal sequence of events? Is it not normal for a diabetic to exhibit glycosuria, for a cretin to be just what a cretin is, for a malignant tumor to do just what a malignant tumor does, for a schizophrenic to behave like a schizophrenic?—HOMER W. SMITH, *Plato and Clementine*, Morris Herzstein Lecture (III) delivered at the University of California, December 6, 1946.

SUICIDE BY ASTHMA

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WHILE bronchial asthma is primarily an allergic disease, considerable evidence has been accumulated indicating that psycho-biological factors play a significant role in the onset, severity, and outcome of treatment. This paper presents our findings in five patients with asthma who, in spite of all therapeutic efforts, both allergic and psychological, died during asthmatic attacks. In reviewing their records we found certain characteristics which separate them from others who responded favorably to treatment. These five patients showed defects of personality organization of such serious degree as to lead us to believe that while asthma was the cause of death it was used as the instrument for suicide.

According to Zilboorg, every case of suicide must bear clinical evidence of strong unconscious hostility combined with an unusual incapacity for love of others. If these findings are present in a patient in which depressive features appear, suicide becomes a real danger even though the wish for self-destruction may never be expressed.

As you can see from the Table I, four of these five patients had perennial vasomotor rhinitis and nasal polyposis for years before they developed asthma. They were aspirin-sensitive, had a high blood eosinophilia, and did not respond to any treatment, even to steroid agents. It was very difficult to establish effective rapport with them and psychologic findings revealed rigid personalities and overwhelming hostility.

Hostility seems to be of critical importance in many somatic conditions. In previous studies it has been shown that anger is conspicuous in the precipitation of attacks of asthma. It is our impression that in the five patients studied, excessive hostility not only precipitated the attacks, but finally "choked them to death."

CASE REPORTS

Mrs. D. W., aged twenty-one, was first seen during May, 1952, because of asthma of nine years' duration. She was the older of two girls, had been married two years to a man seventeen years her senior and had a three-month-old son. She also had migraine headaches, hives and rheumatic heart disease, and had been in cardiac failure two years previously. This patient assumed an attitude of child-like and coy acquiescence toward the physician, yet simultaneously there was evidence of strong uncontained polymorphous hostility. This was expressed in relation to her illness by an "I challenge you to get me well" attitude. This patient recalled considerable strife between herself and her mother during her youth. She reported that the conflicts began when she developed a "mind of her own" and became particularly

Presented at the Fourteenth Annual Congress of The American College of Allergists, Atlantic City, New Jersey, April 25, 1958.

evident when she refused to meet her mother's perfectionistic demands. Her asthma began with her decision no longer to fight with the mother but to "act like a lady." In her adult years she smugly disregarded recommendations of figures of authority. Because of the rheumatic heart, physicians advised her not to have children but she did bear a child. She was cautioned to avoid over-exposure to dust to which she was sensitive, but instead she insisted on closely supervising the construction of her new home. She drove herself until she became ill and then directed her hostility towards her physician. The patient exhibited superficial insight into the etiology of her illness. Her personality structure was very rigid and her defenses fragile. She rejected psychotherapy. She died during an asthmatic attack in October, 1954.

Mrs. D. C., aged forty-one, was first seen during September, 1953, because of asthma of seven years' duration. She was the youngest of five children, had been married twenty-two years and had three children: twenty-one, eighteen and seven years of age. She stated that her first attack occurred shortly after her youngest child was born. Her attacks of asthma became more frequent and more severe at the time that her twenty-one-year-old son made plans to get married. This patient had given up in the attempt to meet the demands of life, and was using her asthma as a justification for doing so. She recalled that in her early life there had been considerable dissension at home with no affection shown between the parents or by the parents to the children. She was a lonely child and took little interest in school activities. Easily hurt by the anger of others, she would go to her room and cry at the slightest provocation. Her marriage presented the first major satisfaction in her life. With their first two children, she and her husband often enjoyed hiking and picnicking. All this stopped after the third child was born and the asthma began. After the onset of her illness the patient had her husband do all of the housework. She did not however, give up visiting with her friends and having company. Many details of this patient's illness are missing because, in a subtle and hostile manner, she would not attempt to recall events and showed disinterest in the world about her. At no time did she express a desire to recover. She died during July, 1954.

Miss B. E., aged forty, single, was first seen in January, 1954, with asthma of nine months' duration. She was the second of six children and lived with her widowed mother. She was seen for psycho-therapeutic interviews over a period of eighteen months. She maintained a position of responsibility in an office in which she had been employed for twenty-five years. She had a striking need to be independent and on occasion would assert this need in an almost defiant manner. Most uncomfortable socially, she invested herself without limit in her work. The other dedication in her life was the care of her mother, upon whom the patient depended in an infantile fashion when her asthma was severe. The mother's solicitous care was alternated with competitive rejection and disapproval when the patient manifested qualities of mature femininity.

Miss E. drove herself to be strong and adequate in every area of life and resented strongly any intrusion into her well-ordered schedule of living. The asthma began when her life situation grew increasingly taut as her boyfriend of ten years demanded that she marry him and her mother countered with the demand that she give up all men and build a new home for the mother and herself. At the same time, several changes of company policy tended to curtail her occupational gratification. With satisfaction reduced and hostility mounting, the patient's asthma became worse until she died in August, 1957.

The only man in this series, Mr. T. R., aged forty-eight, was first seen during July, 1953, because of asthma of two and one-half years' duration. This man had been studied at the Mayo Clinic, Johns Hopkins, Barnes Hospitals, and by four other

TABLE I. SUMMARY OF FIVE CASES OF SUICIDE BY ASTHMA

Name	Age	Duration of Asthma	Other Somatic Manifestations	Blood Eosinophilia
(1) D. W.	21	12 years	Rheumatic heart disease Migrane headache Urticaria Penicillin-sensitive	18%
(2) D. C.	41	8 years	Vasomotor rhinitis, since age of ten Nasal polyposis Aspirin-sensitive	25%
(3) B. E.	40	3½ years	Vasomotor rhinitis since childhood Nasal polyposis Chronic maxillary sinusitis and ethmoiditis Aspirin-sensitive	20%
(4) T. R.	48	2½ years	Vasomotor rhinitis since childhood Nasal polyposis Disk with spinal fusion Aspirin-sensitive	21%
(5) E. G.	53	3 months	Vasomotor rhinitis, for three years Frontal headaches Sinusitis, for twenty years Physical allergy Sensitive to penicillin, cocaine, vitamin B	4%

physicians. He was the fourth of nine children. He first married at the age of twenty-one. His wife died nine years later and he remarried within a short time. He stated that his symptoms started after his second wife sustained a fractured pelvis as the result of an auto accident and it became necessary for them to change beds. At the time his symptoms were most severe his twenty-four-year-old daughter was married. He was extremely over-active and talked quickly. This patient stressed that for thirty years he had shown an exaggerated independence and aggressive drive in his work. He said this was the way his father had lived and worked. There were strong indications that his wife's inability to satisfy his dependent needs and his awareness that she was seriously incapacitated and that he could not count on her help, served as important stresses in the etiology of his attack. He attacked the physicians whom he consulted in the same manner in which he had worked all of his life by not accepting the advice or recommendations of any physician and by maintaining a belligerent "do or die" attitude toward them. His attitude towards the psychiatric examination was similar—belligerent and resentful, rejecting help offered. He died early in 1954.

Our last patient, Miss E. G., aged fifty-three, was first seen in September, 1956, with asthma of two and one-half months' duration. She gave a history of having developed a vasomotor rhinitis three years previously, following an injection of Vitamin B. She was the third of seven children and lived with an unmarried sister. Miss G. was seen for three interviews over a six weeks' period. Her defiant independence and hostile competitiveness were difficult to penetrate. She was a capable and successful business woman who vigorously denied recognition of any flaw in her concept of herself as an all-sufficient personality. She readily admitted having a case of "nerves," but felt that anyone in her business would be tense. Her asthma would occur suddenly every three to four hours and necessitate a reduction of her rigorous schedule. She said that her asthma was the only cause of "her nerves," although she described (with little affect), night terrors, periods of crying, excessive

fatigue, and outbursts of destructiveness. She said that she was much liked and the center of a large social circle. With all her independence, she was childishly demanding that she be cured completely of her symptoms without the necessity of much investment on her part. Dissatisfactions with various aspects of her life were expressed but without insight into her personal involvement as a causative factor. The narcissistic blow of a referral for psychological evaluation, the lack of motivation to change, and her intense hostility were insurmountable barriers to psychotherapy. She died in 1957.

The Bell Adjustment Inventories completed by four of these patients who died were compared, item by item, with each other and with adjustment inventories completed by ten patients with severe but nonfatal asthma. The series obviously is too small to be statistically significant, but some interesting trends were apparent. Considering the inventories of the four as a group, we see a degree of internal consistency. Generally, the scores indicate a materialistic orientation with a low sensitivity to the patient's own emotions and a limited capacity to appreciate the feelings of others. In contrast to patients with nonfatal cases, the patients who died were unwilling to acknowledge minor emotional conflict within themselves, such as the desire as a youth to run away from home or the occasional feeling of isolation in a crowd. Fear of the dark, various phobic reactions and even day-dreaming were denied! They admitted no difficulties in their interpersonal relationships or other evidence of tension in social situations.

This pattern suggests a strong hostile tendency coupled with a powerful need to maintain a self-concept of strength, adequacy and independence. Compared with the others, they found it difficult to ask for help; however, there were present also qualities of childish demandingness and tendencies to feel hurt. In questionnaires of these four patients, repression was seen as the major defense mechanism. The people left themselves no outlet for their tensions except illness. They would tolerate no deviation from perfection in the emotional, social, physical and vocational areas. One quickly perceived the marked psychological turmoil which they were attempting to contain by their rigid and fragile defenses.

PSYCHOLOGICAL FORMULATION

Psychologically these patients exhibited two basic characteristics, strong dependent longings and an inability to relate satisfactorily to others. There is evidence that these characteristics reflect their early relationships to mothers who alternated over-protectiveness with hostile competitiveness and who blocked the patients' attempts to develop close relationships to them.

Dependency is a major area of conflict, and the pressure of ungratified dependent cravings is a significant force in the development of physical symptoms. These patients were narcissistic, demanding, provocative people who had to deny weakness in any form because their defenses were built around a self-concept of strength and competence. A modicum of gratification was obtained by making others dependent on them, and a compul-

sive solicitousness appeared as a reaction-formation. The constant use of obsessive-compulsive mechanisms attested to the fragility of their emotional equilibrium, which was under continued pressure from the excessive hostility which resulted from blocked dependency.

The defenses of these patients were poorly integrated and began to deteriorate when they were under the impact of an external stress to which they were particularly sensitive. In all cases a shift of environmental forces suddenly reduced important sources of dependent gratification and presented the patients with the problem of handling a relative increase in already excessive dependency needs and hostility. This stress was perceived as a narcissistic insult. Emotional balance could not be maintained and, due to the rigidity of the personality, ego regression did not occur. Asthma was utilized as a way out and at this point a resonating circuit was established.

Through asthma, these patients obtained love in the form of physical attention and care. At the same time, they used illness as a primitive means of expressing hostility. Both of these satisfactions, however, provoked guilt and the need for self-punishment. Again asthma suited the purpose by supplying a masochistic outlet for these feelings. Unfortunately, the handicap also served as a continuing narcissistic injury to the patients' sense of adequacy and consequently was a constant stimulus to further dependency and the concomitant hostility.

Because of the environmental changes which produced ungratified dependent longings, an acceptable level of adjustment was beyond their reach. This was further accentuated by the absence of other mechanisms of adjustment as substantiated by the Bell Adjustment Inventories. The noose continued to tighten as the patients were driven farther and farther from their prior level of adjustment until no return was possible. Death was the only way out as shown by the fact that one of the patients put her affairs in order and then stopped all medication, and another, knowing it would be fatal, took aspirin.

There is no personality profile unique to bronchial asthma; however, the patients presented here had important psychodynamic similarities which clearly set them apart. These similarities we have attempted to describe. The anger which isolated them from warm human contacts throughout their lives created an impenetrable barrier to effective treatment and made the following quotation from Shakespeare's Coriolanus, Act IV, particularly apt:

> "Anger is my meat, I sup upon myself,
> I so shall starve with feeding."

REFERENCE

Zilboorg, Gregory: Differential diagnostic types of suicide. A.M.A. Arch. Neurol. Psychiat., 35:270-291 (Feb.) 1936.

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THE STUDY OF ALLERGIC REACTIONS IN THE ETIOLOGY OF BRONCHIECTASIS

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BRONCHIECTASIS may be defined as a condition of the lungs in which there is a dilatation of the bronchi and bronchioles. Congenital and infectious factors have been considered to be important etiologic factors. Allergic reactions are rarely included in the general medical literature. The purpose of this paper is to help clarify the role of allergic reactions in the pathogenesis of bronchiectasis. The mechanism of bronchiectasis has been described in two recent monographs on chest diseases.[7,8]

The thick tenacious mucus which is found in an allergic bronchitis and asthma may obstruct the bronchi and bronchioles if not removed. Bronchial obstruction may produce localized atelectasis with the following effects:[2,3,6]

1. With the subsequent bacterial invasion of the bronchial wall, the elastic fibers of the central layer degenerate and rupture. As the elasticity of the wall is lost, the bronchi may easily dilate.

2. With the loss of the alveolar air, the atelectatic area becomes stiffened and the movements of the chest cage and diaphragm are transmitted more directly to the fixed area.

3. The trapped secretion may increase the pressure within the bronchial lumen. This, associated with a decreased pressure in the alveolar areas, intensifies the dilatation.

4. Ultimately, fibrotic contraction, secondary to the above chain of events, may produce additional dilatation by traction between the different segments.

Many explanations have been offered for the co-existence of sinusitis and bronchiectasis. After Kartagener's description[5] of sinus abnormalities, bronchiectasis and situs inversus, congenital factors were considered. Drainage into the lungs from infected sinuses can constantly spread the infection into the lower respiratory tract. The coughing of infectious material from the bronchiectatic areas may infect the sinuses. Patients with sinusitis or rhinitis are often "mouth breathers" and do not ventilate as deeply as do individuals who breathe through the nose. Therefore the air currents within the lung may not be great enough to remove any mucous plugs which are present. Lastly, allergic respiratory disease can involve the nose, paranasal sinuses, and lungs simultaneously so that indi-

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viduals with allergic disease of one area of the respiratory tract may have similar pathologic changes elsewhere.[9]

CASE REPORTS

The following cases were selected to emphasize the above statements:

G. P., a fifty-six-year-old metal worker presented a history of asthma since the age of eighteen, persistent cough since thirty-five, and expectoration of foul material for the past ten years. Spooning of the nails and cyanosis have been present for five years. Bronchograms show extensive bilateral bronchiectasis. Eosinophilia appeared in twenty-five per cent of the nasal smears studied.

In this patient, bronchiectasis developed when severe asthma was allowed to progress without interruption. The severity and duration of the asthma were the important factors. The bronchiectasis apparently began years ago when the bronchial plugs were not expectorated promptly.

V. L., a waitress, aged forty-eight, had a history of asthma for twenty-five years, and known bronchiectasis for five years. A bronchogram showed the bronchiectasis. After an acute respiratory infection, the x-ray showed a contraction of the middle lobe of the right lung. The patient improved on antibiotic therapy but the right middle lobe changes did not disappear for several months. This was shown by repeated x-rays.

In this asthmatic patient with bronchiectasis, bronchial plugging initiated the described sequence of bronchial irritation, infection and atelectasis. Middle lobe syndrome due to allergic disease has been described.[1]

R. C., a housewife, aged forty-one, suffered a massive hemoptysis. Her past history included frontal headaches, nasal blockage, and six instances of slight bleeding from the lungs. X-ray of the sinuses showed thickened membranes; the bronchograms visualized bronchiectasis in the right lower lung. The nasal smear showed sixty per cent eosinophils. Allergic management was instituted with partial relief. Two years later the bronchiectasis could not be demonstrated by the bronchogram.

With the institution of allergic management, further damage to the lungs has been prevented. With the decreased bronchial irritation, the reactions were reversible. Reversible bronchiectasis has been described.[3,4]

C. S., a twenty-four-year-old secretary, had a chief complaint of hemoptysis. Physical examination and bronchograms were negative. Bronchoscopically, the mucosa was pale and swollen. The nasal smear showed 65 per cent eosinophiles.

This patient has allergic rhinitis but no bronchiectasis. This patient is included because of the similarity to R. C. except that the pathologic changes had not progressed as far.

E. H., a woman, aged thirty-eight, suffered from asthma and had a chronic cough with the expectoration of much foul smelling sputum. She had some relief with allergic management. Later the right lower lobe of her lung was removed after a diagnosis of bronchiectasis. Pathologically, the tissue showed changes consistent

with bronchial asthma. Postoperatively her symptoms were not improved until allergic management was reinstituted.

This case demonstrates that sometimes there is difficulty in the differential diagnosis between asthma and bronchiectasis. It is important to treat each disease, if both are present in the same patient. It has been noted that patients with bronchiectasis who move to arid lands still may suffer from allergic respiratory disease.[10]

Furthermore, this case emphasizes the judgment which must be used in the selection of cases for surgical treatment. The criteria for segmental resection must be carefully observed. Also, allergic respiratory disease, if present, must be fully controlled before surgery is considered.

CONCLUSIONS

Bronchiectasis and allergic respiratory disease are often co-existent.

Allergic bronchial exudation with bronchial plugging by inspissated mucus may initiate the cycle of events leading to bronchiectasis—atelectasis, secondary infection, and weakening of the bronchial walls.

Allergic factors, by a similar mechanism, may play a role in the pathogenesis of the middle lobe syndrome.

When allergic factors and bronchiectasis co-exist, the bronchiectatic process may be reversed by the prompt institution of allergic management and treatment.

The differential diagnosis of bronchiectasis and bronchial asthma may be very difficult but it is important, from the standpoint of therapy and prognosis, to determine the presence of one or both.

Before pulmonary surgery is considered, the recognition and management of allergic factors is of major importance. Control of the allergy aids in the selection of cases for resection and may arrest the process causing bronchiectasis elsewhere in the lung.

REFERENCES

1. Abram, L. E., and Frankl, J. S.: Pneumonitis and atelectasis occurring in the course of allergic disease. Ann. Allergy, 14:360, 1956.
2. Andrus, P. M.: Bronchiectasis. Am. Rev. Tuberc., 36:46, 1937.
3. Fleishner, F.: Pathogenesis of Bronchiectasis. Am. Rev. Tuberc., 42:297, 1940.
4. Hinshaw, N. C., and Garland, L. H.: Diseases of the Chest. Philadelphia, Pennsylvania: W. B. Saunders Co., 1956.
5. Kartagener, M.: Zur Pathogenese der Bronchiektasien; Bronchiektasien bei Situs viscerum inversus. Beitr. z. Klin. d. Tuberk., 83:489, 1933.
6. Riggins, H. D.: Present concepts of pathogenesis, morbidity, mortality, and treatments of bronchiecetasis. Dis. Chest, 9:5, 1943.
7. Segal, M. S.: The Management of the Patient with Severe Bronchial Asthma. Springfield, Illinois: Charles C Thomas Co., 1950.
8. Segal, M. S., & Dullano, M. J.: Chronic Pulmonary Emphysema. New York: Grune & Stratton. 1953.
9. Thomas, J. W., Van Ostrand, H. S., and Tomlinson, C.: Treatment of bronchiectasis with chemotherapy and allergic management. Ann. Int. Med., 23:405, 1945.
10. Watson, S. H., and Kibler, C. S.: Bronchiectasis. J.A.M.A., 111:394, 1938.

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THE TREATMENT OF BRONCHIAL ASTHMA WITH MEDROL

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THE purpose of this paper is to discuss the initial experiences in the treatment of severe chronic bronchial asthma with Medrol*. Medrol differs from Prednisolone by having a methyl group attached in the Delta 1 position, and initial pharmacological studies on both animals and humans have shown that Medrol is approximately twice as potent as Prednisolone, and there is some evidence that it has less sodium retentive effect and may cause less gastric irritations. It is approximately ten times more potent than Hydrocortisone. The pharmacologic studies on the effect of water and sodium retention show that Medrol in the clinical doses used has little or no mineral corticoid activity as far as sodium retention or the holding of water in the intercellular spaces is concerned. The biological half-life of Medrol was 1.5 and 1.4 times that of Hydrocortisone and Prednisolone, respectively.

The twelve cases selected for study with Medrol represented allergic bronchial asthma of a mixed type. Ages range from twelve to fifty-one years of age. All of these individuals had a history of bronchial asthma for many years. Two of the patients whose cases are reported in detail had asthma related primarily to ragweed sensitivity with some element of mold sensitivity. Two other cases reported in detail were examples of multiple inhalant sensitivity to various seasonal pollens, several of the molds, dust, animal danders and feathers. All twelve patients represent severe chronic asthma of a mixed intrinsic and extrinsic type. Four representative cases will be reviewed in detail. In only one patient, a twelve-year-old boy, was there any other associated pathology. This boy represented an advanced case of kyphoscoliosis due to congenital abnormality of the cervical-dorsal vertebra. He had an attempt at corrective orthopedic surgery at six years of age, but has a grossly deformed thoracic cavity. Other than this anatomical deformity, this individual was normal. The four cases in which Medrol was used are presented in detail and will be summarized later. In all twelve cases in which Medrol was used, the only other adjunct was the use of standard pharmacologic preparations for the control of the asthmatic episode. No other corticosteroid was used or had been used for thirty days prior to the administration of Medrol. Antihistamines on some occasions were used, but reliance was placed primarily on the use of proprietary anti-asthmatic preparations for relief. Two of the patients among the four cases discussed had been receiving desensitization therapy

*Medrol is Upjohn Company's brand of Delta 1, 6-methyl-hydrocortisone.

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for pollens, dust, and molds. However, one of these two patients had just started therapy in mid-summer. One patient had been on therapy for about one year. The dose of Medrol that was used was 2 mg tablets, scored, and the initial dose used in all individuals was three tablets for the first three days and if, as in four instances, there was significant relief of the asthma, the dose was further reduced. The average dose in these individuals was two tablets a day or 4 mg.

CLINICAL SUMMARIES

Case 1.—W. G., twelve-year-old boy. History of severe chronic bronchial asthma since five years of age. This boy has kyphoscoliotic thoracic deformity due to congenital abnormalities in the cervical and upper dorsal spine, as well as seasonal hay fever in Spring and Fall, chronic allergic rhinitis, periodic migraine headaches, and almost constant moderately severe to severe bronchial asthma. Skin testing by scratch and inter-dermal method showed this boy to be sensitive to multiple Spring, Summer and Fall pollens, Alternaria, Aspergillus, Fusarium, Helminthosporium, Hormodendrum, house dust, multiple sensitivity to animal danders, insects and feathers. Food did not seem to be a provocative agent in his asthma though it was felt that milk and chocolate precipitated his migraine headaches. The patient was on desensitization for the seasonal pollens for the dust and the mold and the feathers, and had done fairly well. However, in August of 1957 to mid-September of 1957 the pollen count for ragweed became extremely high, reaching 700 to 1200 grains per cubic yard of air. At the same time the regional alternaria count became quite high. At this time the boy contracted a mild upper respiratory infection of a viral nature. Apparently the combination precipitated acute and severe asthma which soon became refractory to proprietary anti-asthmatic drugs, and the patient was placed on small repeated injections of Broncheprine® for relief. However, in spite of this he had severe asthma and hospitalization was considered. However, prior to hospitalization the patient was placed on three tablets of Medrol, 2 mg, one every eight hours for two days, later reduced to two tablets a day. At the end of the second day the asthma seemed appreciably better although there was still some clinical evidence of asthmatic breathing. In another twenty-four hours, however, the chest seemed perfectly clear and the boy was able to return to school. There was no evidence of asthma, hay fever or allergic rhinitis, in spite of the high pollen count for both ragweed and alternaria. The viral infection was treated with broad spectrum antibiotics primarily because we were using corticoid steroid on this individual. After two days of 2 mg daily, the dose was reduced to one tablet daily in divided doses and he has remained on one tablet since the onset of this severe asthma and at the writing of this report has remained entirely asthma-free. The desensitization program has continued. The antibiotic therapy has ceased. There is no clinical evidence whatsoever of any asthmatic process. No studies were done for vital capacity or other respiratory changes because of the short duration of the therapy.

Case 2.—T. W., a man, aged twenty-six, gave a history of chronic recurrent, perennial asthma for over twenty years. This patient had been under the treatment of various physicians for chronic, perennial allergic asthma for over twenty years. On several occasions desensitization had been attempted but apparently was never successful, due to the fact that the patient moved about a great deal and saw a number of physicians. When first seen he was a college student in graduate school and was having daily, mild asthma. Occasionally the asthma would become severe enough to require an injection of adrenalin, which he had administered to himself over several

years. This person, however, "lived on Tedral" and was able to continue his studies fairly well. Skin testing showed multiple reactions to all of the Spring, Summer and Fall pollens, molds, dusts, danders, insects and foods, but the patient declined to have desensitization at this time, preferring to try Medrol in place of the desensitization. He was consequently placed on three 2 mg tablets of Medrol a day for three days. At that time there seemed to be definite improvement of his bronchial asthmatic condition. The Medrol was then reduced to two tablets a day. Two days later (a total of five days on Medrol therapy), there was no evidence of asthma in this individual. He felt extremely well and according to him he was entirely free of respiratory difficulty. The patient was continued on two Medrol tablets daily for two weeks, and because he seemed to be doing well was reduced to one a day in divided doses. In late July there was a flare-up of asthma, associated with an intercurrent respiratory infection and perhaps some increase in the mold count at that time. The ragweed pollen count was zero. At that time the Medrol was increased to two tablets daily and within two days this mild flare-up was under control and he was able to reduce the dose to one tablet daily after four days. In late August, when there was a marked rise in the ragweed pollen count, the asthma again became moderately severe and the patient, on his own, increased his dose to two Medrol tablets daily. He reported two days later that he was entirely free of hay fever and asthma. We were able to carry him through the acute peak of the ragweed season with two Medrol tablets daily, and the patient has remained entirely well. Originally this patient had had some pulmonary function studies done at a hospital pulmonary laboratory, the reports of which were not available to us at the time. These reports were, however, summarized for us, and showed definite decrease in vital capacity, but no gas diffusion abnormality.

Case 3.—P. M., a sixteen-year-old boy. This young man had had moderately severe asthma for the past seven to eight years, which gradually became more severe during the last three years. There has never been any therapy other than the use of proprietary anti-asthmatics. The patient presented himself to us this Spring with moderately severe asthma, enough to interfere with his high school education. He was at that time taking Ambec and Benadryl for relief with rather incomplete results. The patient had been studied on numerous occasions in the past and was again studied by us with scratching and interdermal skin testing, which disclosed moderate reactions to seasonal pollens, particularly those of the Spring and Fall, marked reactions to molds, dust, animal danders, and feathers. No food sensitivity was demonstrated. The results of our skin testing corroborated skin testing done in the past. We decided to start this patient on a program of multiple desensitization for the seasonal pollens, dust and molds. This was started in late Spring. However, at the time, the patient has considerable asthma and for relief was placed on Prednisolone, 2.5 mg tablets, three times daily and he derived considerable benefit from this, which controlled his asthma sufficiently and allowed him to finish school. It was necessary to continue Prednisolone therapy for two weeks, and because he was entirely free of asthma and the Spring season was ending, the Prednisolone was stopped. He remained quite well during the early Summer months. In mid-July, however, he began to complain of asthma while on a visit to a farm. This asthma was to such a degree that it necessitated his leaving the farm and returning home. The asthma did not clear up, however, and became worse. The patient was in severe asthmatic distress when it was decided to re-institute corticoid steroid therapy. At this time the patient was placed on 2 mg tablets of Medrol every eight hours for two days. At the end of the second day there was definite clinical improvement in the asthma, and with reduction of Medrol therapy this continued. Because of a flare-up of asthma with the appearance of high ragweed pollen this Fall, the patient

was continued on Medrol in minimal adjusted doses through the hay fever season and had only one small flare-up prior to the adjustment of his dose, and this was brought under control in twenty-four hours. He has remained asthma-free and has been able to start the Fall term of school without any loss of days.

Case 4.—W. P., thirty-six-year-old man presenting a history of asthma for six years, primarily during the Fall and Winter months. This individual has had mild asthma which usually starts with the hay fever season and extends through Winter. Skin tests disclosed sensitivity to the Fall pollens, especially the hay fever group, and also to dust and molds. The patient presented himself for study the first of August, and because it was too late to start on hay fever desensitization, we elected to use Medrol through this first season to evaluate the results, starting him on desensitization the following year. The patient was started on three 2 mg tablets daily for three days and then reduced to two 2 mg tablets. The asthma which he had at this time was very minimal. With the onset of the therapy the asthma was under control in twenty-four hours and he has had no asthma during the hay fever season at all. This is the first year in which he has been entirely free of both hay fever and asthma, and has been able to continue work uninterrupted. During the last two years the patient had received Prednisolone therapy, but with such therapy still had a moderate amount of hay fever and asthma.

The four cases discussed above were representative of the total series of twelve severe asthmatic patients in whom Medrol was used. Each of these presented severe, chronic asthma of many years' duration, due to extrinsic and intrinsic factors and of a complex nature. The eight additional cases which will not be summarized here were divided as follows: five men and three women. The ages were eighteen, twenty-one, twenty-nine, thirty-three, forty-one, forty-eight and fifty-one years. All of these patients had been receiving treatment with dust, mold and various seasonal pollen vaccines. However, these patients all represented early treatment cases in our hands, and had no vaccine therapy under our direction for longer than twelve weeks. When the physicians in this area heard that we were using a new corticosteroid in the treatment of severe asthma, we received several chronic asthmatic patients for study in the hope that this might help them through the severe phases of their asthma. Several of these patients had been under treatment of various physicians and had received both specific and non-specific anti-asthmatic treatment. Most of them were somewhat discouraged with their progress and felt that they had a basically incurable disease. It is to be pointed out here that all of these patients were subjected to thorough studies and were started on basic anti-allergic measures consisting primarily of desensitization for their asthma. Foci of infection of the upper respiratory passages were diligently sought out and eliminated. Medrol was used in these patients only to carry them through acute exacerbations of their asthma and to afford them relief when they were in advanced asthmatic states. These eight additional cases will not be discussed in detail other than to reiterate that they represented advanced chronic asthma in which Medrol was used to carry them through acute exacerbations.

TREATMENT OF ASTHMA WITH MEDROL—WYGANT

SUMMARY

This is a preliminary report of twelve individuals with varying degrees of chronic allergic asthma who were treated with a new corticosteroid, Delta 1, 6-Methyl-Hydrochloride, marketed under the trade name Medrol. The relationship of Medrol to Prednisolone is mentioned briefly as having been demonstrated as approximately two times stronger in the oral route.

CONCLUSION

It was felt that, in this early study on twelve cases, Medrol presented very definite and striking anti-allergic manifestations, giving excellent and rapid remission of asthma in the cases studied. No side effects were noted at any time.

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Submitted March 30, 1958

THE TARDY CONVALESCENT

Recently I found myself addressing a professional invalid in these words:

"Are you quite sure you really want to get perfectly well? Supposing I could wave a magic wand over you and make you fit, just think what it would mean. It would mean giving up bossing people around and making them fit in with your wishes. You'd have to find other things to talk about, other things to think about. *You might even find yourself having to do things for other people.* The sacrifices would be terrible. You've quite forgotten what it is like to be well. Are you sure you can make this sacrifice? I don't want your answer now. Think it over. Sleep on it. Take your time. I'm in no hurry. If you really want to get well, I think I can help you to help yourself. But you'll have to do all the work. There's no magic wand."

I wouldn't listen to any expostulations, but bade her sleep on it.

She didn't sleep very well that night. The next morning, when she told me she really did want to get well, I just shook my head in disbelief, and there I let the matter drop.

The days went by. She made a perfectly good convalescence. As she crossed the front hall carrying her suitcase to the waiting car and I went across to say good-bye, she turned on me in front of all the other patients loitering there:

"You are a fine doctor, I must say, talking to me as you did when I first came here. I've never heard the like. I shan't come back here in a hurry."

I bowed my head in shame. She got well to spite me.

—GEORGE DAY, M.D.

SOME THOUGHTS ON THE NATURE OF ALLERGY

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DURING the past fifty years, active research in the field of allergy and hypersensitivity has accumulated an enormous body of facts. Yet the most fundamental question, the biologic significance of allergy and its relationship to immunity, remains in the realm of theory much as it was in 1902 when Richet discovered anaphylaxis while attempting to produce immunity to actinia toxin.

It is this subject that I wish to consider. Much of the discussion will be theory rather than fact. Theories are guides useful in directing our thoughts, but subject to change as new facts are accumulated.

In discussing allergy, I shall limit my attention to a few typical forms in which the immunologic mechanism is reasonably well established: anaphylaxis and atophy—as examples of the immediate reactions; the tuberculin reaction and contact dermatitis—as examples of delayed reactions.

Regardless of their immunologic mechanism, the phenomena of allergy may be divided into those manifestations which are readily produced in practically all individuals of the species by some definite sensitizing procedure and those that develop "spontaneously" in individuals of a particular genetic constitution (atopy). The former are normal physiologic reactions of the species to certain conditions; the exact nature of the latter is less apparent, but they may be presumed to represent an hereditary aberration of the immune mechanism. The physiologic allergies are associated with the development of the same types of antibodies involved in immunity. It is readily shown that the same rabbit antipneumococcus serum that produces immunity to infection in the mouse produces anaphylactic sensitization in the guinea pig. On the other hand, atopy is mediated by an unusual antibody which ordinarily has no apparent protective function.

I say "ordinarily" since Kuhns and Pappenheimer[1] have reported that atopic individuals injected with diphtheria toxoid may develop antibodies which are skin-sensitizing and which also neutralize toxin. There is some doubt whether both of these properties of the serum are due to the same antibody but this is not important to our discussion since it is so apparent that most atopic antibodies have no such protective function.

Among the most distinctive characteristics of life are the self-perpetuation of the living organism and of its species' individuality. The chemical composition of protoplasm includes water and salts which also

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occur in mineral matter and compounds such as glucose and organic acids which are formed as a result of life processes but are common to a wide variety of organisms. The actual life processes and the differentiation of the species of organisms depend upon the presence of proteins (and complex carbohydrates) which alone have the variety of chemical structure to permit differentiation of species, its perpetuation by genes and specific enzyme actions. The continuation of the individual organism and of the species may be said to depend upon the maintenance of the characteristic protein content of the protoplasm.

Such simple forms of life as the ameba, maintain their protein constitution by differentiating sharply between their own body protein and that of foreign species. Their nutrition and growth depend upon the assimilation of protein formed by other organisms, but when these foreign proteins are engulfed by the cell body, they are promptly broken down by enzyme action into simple amino acids. This digestive process serves simultaneously to supply material for the synthesis of ameba protein needed for growth and reproduction, to preserve the specific nature of the protein of the cell body and to prevent the growth and reproduction of smaller parasites within the ameba.

In more complex animals, these same functions are performed but by various specialized cells. The digestion of protein normally ingested as food is carried out by certain organs derived from the endoderm which deliver nitrogenous nourishment to other tissues of the body in the form of amino acids. However, certain mesodermal cells outside the digestive system retain the property of distinguishing between body protein and foreign protein which has gained access to the system without digestion, such as invading microorganisms. When foreign protein comes into contact with these cells, they react by forming a modified body protein—antibody—which specifically combines with the foreign material as a first step in its elimination. This reaction of antibody formation results from the presence of foreign portein regardless of whether it is a living organism or lifeless material and also of whether it is an active toxin or merely a threat to the uniformity of body protein. Indeed, the newer knowledge of autosensitization indicates that certain specialized proteins of the body itself, (when out of their usual place), may be treated as foreign material.

If the same antigen again enters the body, its persistence is prevented by reaction between it and the antibody. If the antigen reacts with antibody attached to cells, the reaction causes physiologic disturbances of the cells involved. On the other hand, the reaction between antigen and circulating antibody causes little or no disturbance of function. The over-all effect of the antigen-antibody reaction is one of immunity, protecting the animal against the persistence of foreign protein in its body. The disturbances of function, resulting from the reaction of antibodies bound to the cells, which may be fatal to the cells involved, or if they are

cells of a vital structure, to the animal itself, are the manifestations of sensitization.

The extent of this disturbance of function depends upon the balance between circulating and cellular antibodies, the amount of antigen entering the body, and its route of entrance. In most natural contacts with antigens, as in ordinary bacterial infection, the amount of foreign protein entering the body is extremely small, the route of entrance through the skin or mucosa and the antibody reaction protects the animal as a whole with slight or negligible tissue damage. The severe and fatal manifestations of sensitization generally result from artificially imposing upon the immune mechanism conditions to which it is not adapted. In anaphylaxis, the shocking dose of antigen, small by ordinary standards, is still far greater than the amounts of antigen in material gaining access to the tissues by natural means, except in such conditions as bites and stings of venomous snakes and insects. The most effective route of eliciting anaphylactic shock, intravenous injection, artificially evades the tissues in which defense against naturally encountered antigens most often takes place. Even under such extreme conditions, animals surviving one or more shock doses rapidly become less susceptible to anaphylaxis or "immune" to ordinary amounts of antigen, by the development of larger amounts of circulating antibody. However, even after they are highly resistant to general anaphylyactic shock, they show violent local reactions to antigen injected subcutaneously or intracutaneously. These routes bring the antigen into direct contact with sensitized tissues without the possibility of admixture with circulating antibody.

Anaphylaxis and immunity, therefore, represent injurious and protective effects of the same antibody mechanisms and under most circumstances occur together. With the usual naturally-occurring exposures to antigen, the protective effects predominate, but in extreme conditions, usually artificially imposed, to which the antibody mechanism is not adapted, the injurious effects may predominate.

The relationship of bacterial allergy of the tuberculin type to immunity has long been debated without conclusive results. In the demonstration of the Koch phenomenon, virulent tubercle bacilli injected subcutaneously into a normal guinea pig spread rapidly to involve the regional nodes. Development of a lesion at the site of inoculation requires about two weeks, but leads to a persistent and spreading ulcer. A similar injection into a previously tuberculous guinea pig produces a shallow ulcer within two or three days, but this heals rapidly without involvement of the lymph nodes. The classical view was that the allergic reaction favored immunity by evoking a rapid inflammation and hindering the spread of infective organisms. However, in this type of experiment the effects of allergy cannot be separated from other factors in immunity, such as the circulating agglutinins and bacteriotropins known to be developed in tuberculosis.

Rich and his associates attempted to distinguish between the effects of allergy and immunity in a series of three experiments in rabbits. (1) They found that in infections with Treponema pallidum, immunity was developed without detectable allergy.[2] (2) From rabbits rendered highly allergic and immune to pneumococci by repeated injections of killed organisms, it was possible to transfer effective immunity to normal rabbits by injection of serum, without transfer of the allergic reaction.[3] (3) They also demonstrated that rabbits highly allergic and immune to pneumococci or Pasteurella aviseptica could be desensitized by injections of vaccine without lessening their immunity.[4] These studies led Rich to the conclusion that bacterial allergy was unrelated to immunity and was a purely harmful rather than protective phenomenon. However, it is worthy of note that in none of these studies was allergy present without co-existing immunity.

The problem is difficult because all organisms which have been studied contain a number of distinct antigens, some protein and some carbohydrate, any of which may stimulate the formation of specific circulating or cellular antibodies in the infected host. In many cases, one of the many antigens present appears to determine pathogenicity and the corresponding antibody is the major factor in resistance to re-infection. For example, in the pneumococcus, infectivity is related to the type-specific capsular carbohydrate and immunity is primarily dependent on the circulating antibody specific for it. It was this circulating antibody which Rich transferred from vaccinated to normal animals in his second experiment cited. The allergic reaction, presumably mediated by a cellular antibody, was not transferred in the serum and was not essential for effective immunity. In other infections, such as brucellosis, the cellular reaction appears to be the main factor in immunity.

It is apparent that bacterial allergy and resistance to re-infection are both manifestations of the development of circulating or cellular antibodies to antigens of the infective organism. All of these antibodies have the property of specifically binding the corresponding antigens. Since certain antigens are more important in the pathogenicity of the organism, the related antibodies play a major role in protection against re-infection. Antibodies for other antigens of the organism may be of little or no practical value, and, if their reaction with the antigen causes tissue damage, even harmful. As in anaphylaxis, the cells forming antibodies react automatically to the presence of foreign protein or complex carbohydrate antigens, regardless of whether or not they represent serious threats to the organism.

The possible beneficial effects of sensitization of the contact dermatitis type to agents not toxic on first contact are perhaps less apparent. It should be recalled that this type of allergy results from entering through the skin of foreign protein or, more frequently, of some substance which combines with the body protein to so alter its character that it no longer

retains its specificity. The formation of antibodies to this foreign or altered protein may be considered a part of the property of the organism of maintaining the specific nature of its protein content. When the same agent again penetrates the skin, the antigen-antibody reaction and ensuing inflammation limit its spread in the body, and slough off the outer layers of skin most heavily contaminated with the hapten.

Thus, most of the common manifestations of allergy (with the exception of atopy) represent not the antithesis of immunity, which they seem on first approach, but the deleterious side effects of the immune mechanism in carrying out its normal function of protecting the body from the entrance of foreign protein material. These injurious effects under conditions of natural invasion by antigenic substances are usually mild, but may be severe or even fatal when the organism is artificially exposed to antigen in unusual quantities or by routes to which the mechanism of immunity is not adapted. From this viewpoint, the apparent paradox of a normal organism encountering a harmless substance and acquiring a violent sensitization to it becomes less perplexing.

The biologic significance of atopic sensitization is more difficult to evaluate. This form of allergy stands out from those previously discussed in several respects. The influence of heredity is much greater, and perhaps essential for its development. Sensitization develops through the slightest and most normal contacts with the allergen. On the other hand, it is difficult or impossible to artificially induce sensitization of this type to a given antigen in previously atopic or in normal individuals by injections or other exposure. Finally, the skin-sensitizing antibody mediating the sensitization differs from other antibodies in chemical properties, does not precipitate the antigen, and is devoid of any known protective value, although the atopic individual is capable of developing a type of apparently protective antibody, the blocking antibody, when the same antigen is introduced parenterally.

The most logical explanation of the known facts appears to be that atopy represents an hereditary abnormality of the immune mechanism of the body. Certain cells of the atopic individual respond to various antigenic stimuli by producing an abnormal or imperfect form of antibody, without apparent protective value, but capable of reacting with antigen to produce deleterious effects essentially similar to those caused by the reactions of antigen and ordinary antibodies in anaphylaxis. Under most conditions the observed reaction to antigen is identical in these two forms of sensitization, since it results largely from the actions of histamine which is released in both. However, the two reactions are less similar at the immunologic than the physiologic level. In anaphylaxis, an excess of circulating antibody usually protects against small amounts of antigen, while in atopy, circulating antibody has not such action. The differences are also apparent in the difficulty or impossibility of rapidly desensitizing the atopic individual by the methods which are applicable to anaphylactic

sensitization of comparable degree. Atopy may be said to be the reaction of an abnormal immune mechanism to normal contacts, anaphylaxis the reaction of a normal immune mechanism to abnormal contacts. This concept may help to guide our thinking in seeing the relationship between the two phenomena.

REFERENCES

1. Kuhns, W. J., and Pappenheimer, A. M., Jr.: Immunochemical studies of antitoxin produced in normal and allergic individuals hyperimmunized with diphtheria toxoid. Part I and Part II. J. Exper. Med., 95:363, 375, 1952.
2. Rich, A. R., Chesney, A. M., and Turner, T. B.: Experiments demonstrating that acquired immunity in syphilis is not dependent upon allergic inflammation. Bull. Johns Hopkins Hosp., 52:179, 1933.
3. Rich, A. R., and Brown, J. H.: Dissociation of allergy from immunity in pneumococcus infection. Proc. Soc. Exper. Biol. & Med., 27:695, 1930.
4. Rich, A. R., Jennings, F. B., and Downing, L. M.: The persistence of immunity after the abolition of allergy by desensitization. Bull. Johns Hopkins Hosp., 53:172, 1933.

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OF NATURE

Nature is a term with many meanings. Three aspects may be defined as follows: (1) our natural surroundings—inanimate nature; (2) animate nature—human nature; (3) the natural state of man as opposed to the higher state of civilization. We know that the third of these has a certain spiritual and intellectual quality; in the natural state man's vision is perhaps somewhat limited, but perhaps also there is a certain trustworthiness about natural man which is partly deliberate but partly also the consequence of his lacking the imagination and factual information he needs to become untrustworthy. There is such a thing as unspoilt human nature even today.

Science, in approaching nature in these three guises, alters it a bit, disturbs it a bit, and perhaps builds something new. Nature, animate and inanimate, is no longer seen as an elemental force; with the help of mathematics abstract laws are formulated, laws already established by experiment. Experiment has already broken up the natural order of things; it isolates one sector and in this isolation it prepares the case which man has determined to treat as a "single" case: whether because this word "single" has some real intrinsic meaning or simply because it best suits our intellectual make-up. Experiment and speculation break up the natural order and rebuild nature on new lines.—PROFESSOR C. F. FREIHERR VON WEIZSÄCKER, *Some Fundamental Problems of Natural Science*, Geigy Bicentenary Scientific Day. Report of the Meeting, June 3, 1958, Basle.

EXHIBIT—MECHANICAL AIDS AND DRUGS

Bronchial Obstruction and Bronchospasm

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1. WHAT TO DO

IN GENERAL, both bronchial obstruction (pathology shown, Figs. 1-3) secondary to either the accumulation of secretions in the tracheobronchial tree or inflammatory changes of the tracheobronchiolar mucosa and peribronchial and peribronchiolar tissue, and bronchospasm are followed by: narrowing of the airways, increased resistance to air-flow, increased work of breathing, alveolar hypoventilation, inadequate oxygenation of the pulmonary capillary blood and interference with the elimination of carbon dioxide—the concept of progressive pulmonary insufficiency (Fig. 4).

Every attempt should be made to determine the responsible antigents. If a detailed history is inconclusive as to the cause of a patient's bronchial asthma, then scratch and intradermal testing shall be resorted to. Removal of the offending allergen (allergic cleanliness) and a trial with specific hyposensitization should be promptly instituted in all cases whenever possible (Fig. 5). Further therapy should be directed towards removing the contributory factors. *Because search for the responsible agents is difficult and often completely unsuccessful, emphasis on the allergic approach to management should not exclude physiologic therapy.*

The primary aims in the actual management of bronchial obstruction and bronchospasm (summarized in Table I and Figure 5) are: (1) removal of secretions from the tracheobronchial tree by the use of expectorants and detergolytic agents to liquefy and decrease the viscosity of the sputum; (2) the use of mechanical aids such as positioning, tracheal aspiration, bronchoscopy, exsufflation (alternating positive-negative pressures), and tracheotomy to evacuate the airways of their obstructing secretions; (3) the relief of bronchospasm by the use of various bronchodilator sprays and aminophyllin by various routes of administration; (4) the repair and reversal of inflammatory changes in the tracheobronchial mucosa and peribronchial and peribronchiolar structures by the use of antimicrobial agents

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This exhibit was prepared by the staff members of the Lung Station (Tufts) and the Department of Inhalation Therapy at Boston City Hospital, based on their own studies, A.M.A. Meeting, New York City, June 1957.
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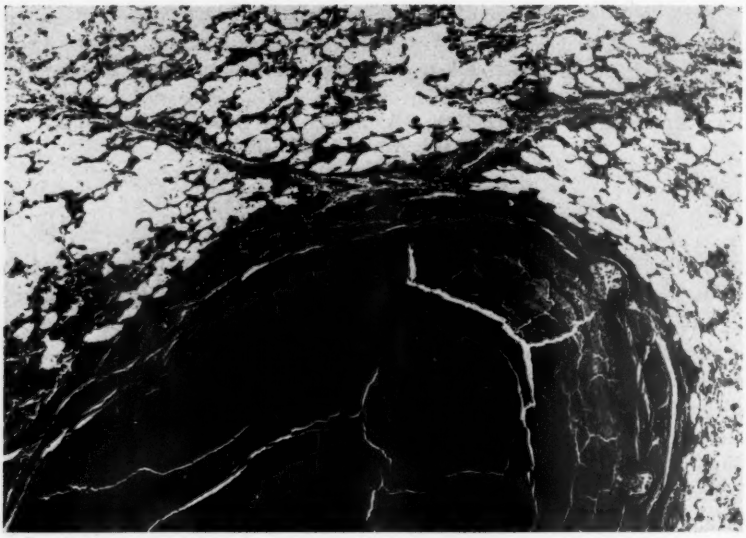

Fig. 1. A medium-sized bronchus containing a mucous plug. Sacculations of the epithelium are present. Bronchus surrounded by emphysematous lung. Magnification: × 27.5.

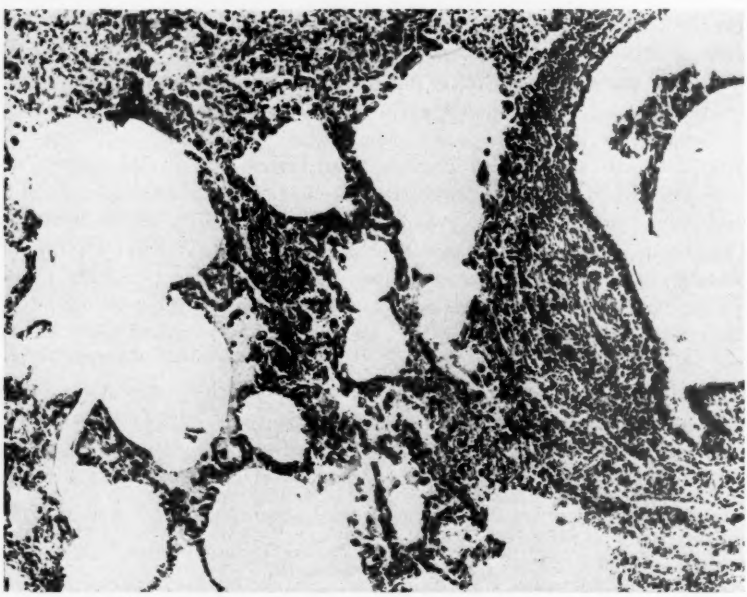

Fig. 2. High-powered photomicrograph of a bronchiole and adjacent alveoli showing: (1) Thinned epithelial lining of bronchiole, (2) Chronic inflammation in peribronchiolar spaces, (3) Destruction of smooth muscle, (4) Emphysematous alveoli.

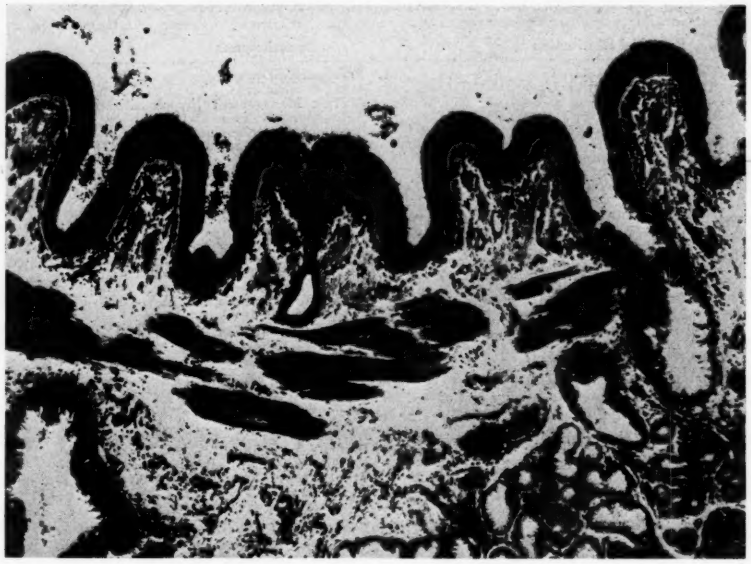

Fig. 3. A medium-sized bronchus showing many distended goblet cells, folding of the epithelium, thickening and hyalinization of the basement membrane, infiltration of lymphocytes, plasma cells and scattered eosinophiles in the lamina propria, active mucous glands and a prominent muscular layer. Magnification: × 27.

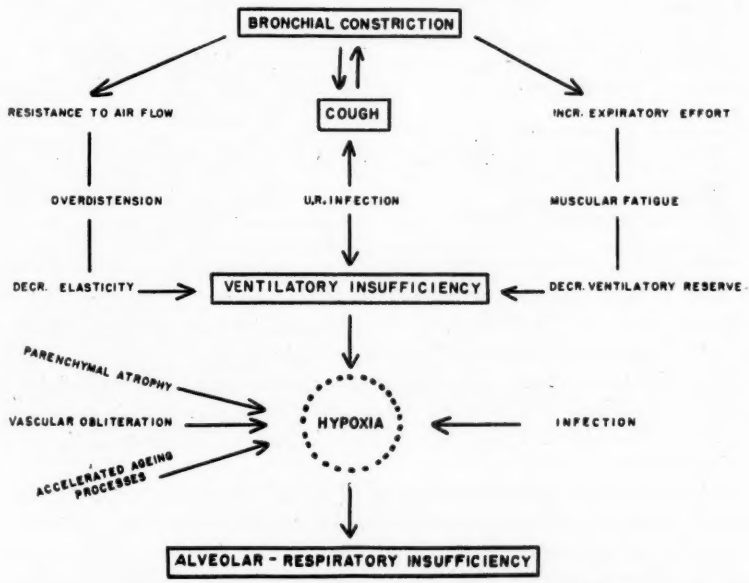

Fig. 4. Progressive evidence of pulmonary insufficiency.

TABLE I. THERAPEUTIC MANAGEMENT

Bronchial Obstruction	Bronchospasm
1. *General Measures* Antitussives (Restrictive Use): Noscapine Dihydrocodeine Tessalon Demerol Medihaler (Dihydrocodeinone; Narcotine; Benzocaine; Hydrocortisone) Expectorant Mixtures: Pyribenzamine Expectorant Hydryllin Compound Fluids (D/W/S): P. O. and I. V. Iodides: P. O. and I. V. Combined with Arsenic Hazards of: Ipecac: Syrup Ipecac	1. *Preventive Measures* Allergic cleanliness Allergic Management (hyposensitization) Antitussive Measures Breathing Re-education Environmental Controls: Dusts Fumes Vapors Smogs Humidity Temperature, etc. Occupation Pre-employment (P. E. and X-rays) Role of Tobacco Seasonal Antimicrobial Chemotherapy Trigger Mechanisms: Chronic Sino-bronchitic Disease Adenoid Tissue Nasal Polypi Physical Factors Emotional Factors
2. *Bronchodilator Aerosols* Adrenergics: 2.25% Racemic Epinephrine Isoproterenols—(Isuprel; Medihaler-Iso) Dylephrin—(Racemic Epinephrine and Atropine) Nebu-Prel (Isoproterenol—phenylephrine) Anticholinergics: Pamine	2. *Treatment of Acute Attacks* Adrenergic-bronchodilator aerosols Aminophyllin I. V. (0.25-0.5 gm in 20 cc or 1 liter) Anti-microbials Epinephrine (aqueous; gels) s. c. Sedation (Demerol; Paraldehyde; Ether) Tranquilizers (Suavitil; thorazine; Trimeprazine (Termaril)) When to hospitalize
3. *Detergo-Lytic Aerosols* Alevaire Alevaire—Water (Alternate) Tergemist (Sodium 2-hexylethyl SO_4) Pancreatic Dornase Hazards of:	3. *Treatment of Chronic (Repeated) Attacks* Bronchodilator Aerosols—Hand Nebulizer or Continuous Technique Aminophyllin— P. O. (Dainites; Cardalin) Rectal (Solutions—Technique) I. V. (Continuous flow—Technique) Anti-microbials Iodides Pressure Breathing Therapy Rehabilitation: Breathing Re-education Job Training Steroids: Prednisolone Meprolone (Prednisolone-Meprobamate) Aristocort (Triamcinolone Diacetate) Decadron Withdrawal Syndrome Hazards and management Sedation Surgical Procedures
4. *Pressure Breathing Therapy* IPPB (with bronchodilator aerosols) P and N (exsufflation)	4. *Treatment Status Asthmaticus* Bronchial Catharsis Cont. I. V. Rx (G/W/S-Aminoph-Nal) Oxygen Helium—Oxygen Mixtures Sedation Steroids
5. *Bronchoscopy* Contra-indications Indications Reactions	
6. *Tracheal Aspiration* Catheter Exsufflation Technique (P and N)	
7. *Tracheotomy* Semi-permanent or permanent in chronic pulmonary suppurative disease Temporary pre- and post-operative patients with limited pulmonary reserve Chronic respiratory acidosis Poliomyelitis and allied disorders Inhalation gas and chemical poisonings	
8. *Positional Drainage*	

(selected according to the predominant bacterial flora and specific sensitivities) and finally, steroid therapy. The latter should be undertaken only after the more conservative measures have failed and with a full understanding of the various side-effects and changes that may occur with this administration and particularly after their withdrawal (Table II). Steroid therapy should represent but a single phase, albeit important, in the total therapeutic program.

As indicated above, the development of alveolar hypoventilation interferes with the adequate oxygenation of pulmonary capillary blood and the elimination of carbon dioxide. Therefore, therapy is directed towards insuring adequate alveolar ventilation, thus preventing or reversing chronic

hypoxia, pulmonary hypertension, cor pulmonale, and respiratory acidosis (Table III) which may follow in its wake.

2. HOW TO DO IT

Antitussive Measures.—The bronchitic cough is one of the most troublesome manifestations and may actually serve as the trigger mechanism for

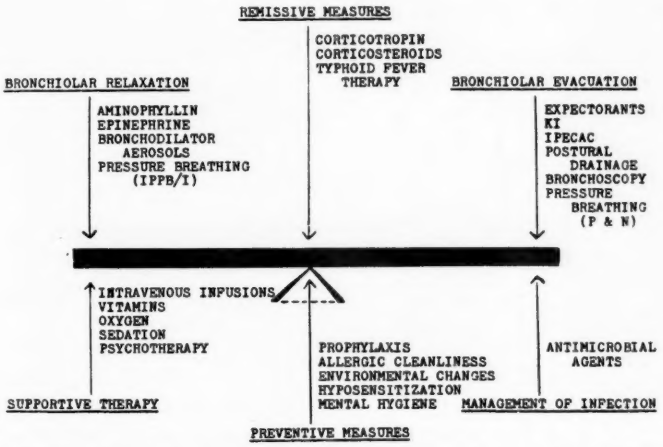

Fig. 5. The therapeutic seesaw in the management of the patient with severe bronchial asthma. (*From* "The Management of the Patient with Severe Bronchial Asthma." Springfield, Illinois: Charles C Thomas Co., 1950.)

TABLE II. CHANGES DURING AND SUBSEQUENT TO CORTICOTROPIN AND CORTICOSTEROID THERAPY

Less Serious:
Facial mooning, acne, edema, hirsutism, skin pigmentation
Headaches, aches, pains, weakness, lassitude
Mild euphoria to mild depression, mental and physical hyperactivity
Hypertension, tachycardia
Hyperglycemia, glycosuria, aggravation of existing diabetes
Depressed thyroid function
Thrombophlebitis
Sensitivity reactions (to intramuscular ACTH)—skin rashes, pruritus, urticaria, occasionally wheezing and angioneurotic edema
More Serious:
Potassium deficiency, muscular weakness
Negative nitrogen balance
Osteoporosis—fractures, especially in women after menopause and immobilized patients
Masked infections, spread of existing infection, serious spread of nonpathogenic inhabitants of the gastrointestinal and respiratory tracts
Mental confusion to severe psychotic manifestations, convulsions
Exacerbation of quiescent ulcers, hemorrhage and perforation in the gastrointestinal tract
Activation and spread of unsuspected or inactive tuberculosis
Sensitivity reaction—anaphylactic shock
Most Serious (Fatal):
Withdrawal syndrome, "adrenocortical storm"
Poor tolerance to trauma, shock and infections
Active atrophy of adrenal cortices

more extensive bronchiolar spasm, expiratory ball valving and alveolar disintegration. The prevention of the serious sequellae of uncontrolled coughing requires a vigorous therapeutic approach. Antitussive agents should be employed to prevent nocturnal coughing paroxysms. We have found very

TABLE III. PULMONARY FUNCTION STUDIES IN CHRONIC BRONCHIAL ASTHMA

Name	Degree of Wheezing	Sex	Age	VC (ml.)	MBC (L. min.)	Res. Vol. TLC (%)	Intra Pul-mon. Mixing (N_2%)	Art. Blood Studies			Compliance (L./cm. H_2O)†		Mean Mech.‡ Resist.				Insp. Time/ Exp. Time	
								pH	pO_2	pCO_2	SR*	FR†	Insp.		Exp.		SR*	FR†
													SR*	FR†	SR*	FR†		
R. W.	0	M	35	4400							0.100	0.608	7.50	—	7.40		0.71	
E. S.	0	M	49	3000	82.5						0.090	0.105	6.95	3.75	13.50	6.55	0.74	0.90
M. G.	+++	F	31	2700	43.3	47.4	3.8	7.40	70	35.0	0.108	0.057	10.90	8.70	21.80	12.00	0.41	0.93
R. J.	++	F	36	2000	68.4			7.39	56	37.5	0.038	0.027	12.80	9.40	16.00	14.80	0.82	0.91
M. F.	+	F	34	2900	65.2	46.4	3.3	7.37	70	38.0	0.190	0.160	3.80	3.80	8.40	4.50	0.75	0.95
M. F.	++	F	34	2100							0.124	0.056	9.70	7.25	11.40	12.90	0.56	0.75
M. F.	++++	F	34	900							0.072	0.062	26.40	7.50	25.40	14.90	0.47	0.84
H. P.	++	M	16	3600	114.0			7.37	80	41.5	0.167	0.131	3.25	3.64	4.25	3.30	0.65	1.00
H. P.	++++	M	16	2500	73.0	60.0	6.0				0.089	0.048	7.20	5.70	9.65	8.45	0.68	1.16
H. P.	+	M	16	3800	103.5						0.100	0.106	4.45	3.00	5.30	3.95	0.63	0.94
Mean				2800	79.0	51.3	4.3	7.38	69	38.0	0.108	0.082	9.30	5.85	12.30	9.05	0.64	0.93
Normal value				3500	164.0	<35.0	<2.5	7.40	>90	40.0	0.140	0.140	3.10	3.40	3.70	3.50	0.80	0.95

*During slow breathing.
†During fast breathing.
‡In supine position.

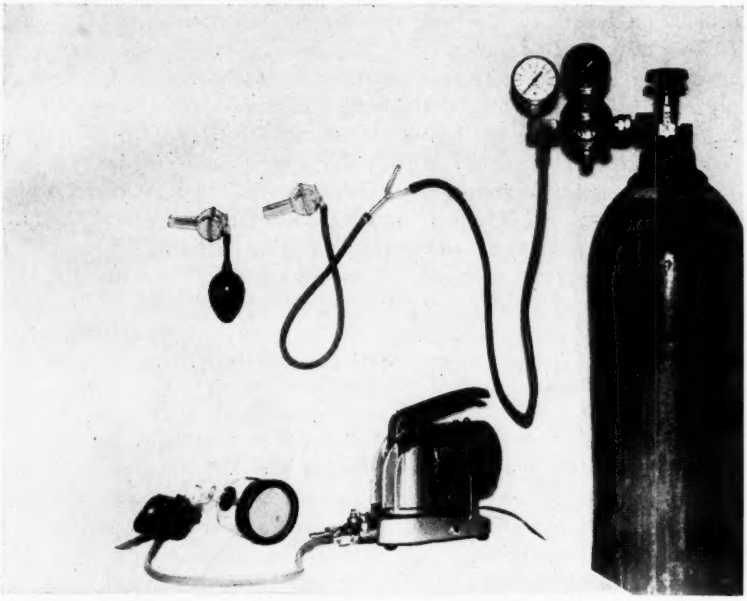

Fig. 6. Intermittent aerosol techniques: Hand Bulb Vaponefrin Nebulizer; O_2-Y Tube—Nebulizer; Eliot Air Compressor, Nebulizer, Face Mask Combination. For agents under 2 and 3 in Table I.

useful three new antitussive agents. Noscapine, an opium alkaloid derivative, is non-toxic and free of respiratory depressing properties. It is suppressive in patients with mild troublesome cough and very useful during the daytime. Dihydrocodeine, a successful analgesic agent, may be employed orally and intravenously for effective suppression of the more serious, hacking, paroxysmal or persistive cough. Tessalon, which may act centrally on the stretch fibers of the pulmonary parenchyma, is more effective when "sipped" in syrup form. Its anesthetic, mucosal effects are pleasantly tolerated by most patients. Its greatest usefulness was observed in patients with annoying tracheal coughs and in children with brief, annoying, nocturnal coughing which interferes with sleep.

Therapeutic Aerosols.—Several methods are available for the administration of adrenergic and detergolytic aerosols (Figs. 6-8). The actual techniques used for the administration of therapeutic aerosols depends to a large extent upon the needs of the patient. For example, the ambulatory patient with bronchospastic disease may simply require the use of the standard Vaponefrin hand-bulb-nebulizer technique or a freon-powered Medihaler-Isoproterenol unit. The hospitalized patient may use the portable Eliot air compressor or similar unit, or the oxygen tank—Y-tube—

nebulizer technique for the brief administration of bronchodilator aerosols (0.5 to 1.0 cc). In nebulizing larger quantities, as with the detergolytic agents, the head enclosed plastic Permatent or plastic Aerosol face tent are preferable. The successful evacuation of tracheobronchial secretions may be observed following the use of continuous aerosols of two new therapeutic preparations: surface tension lowering aerosols of Tergitol with potassium iodide (Tergimist) and aerosols of Pancreatic Dornase. In the presence of bronchial infection, bronchiectasis or viscoid, tenacious, mucopurulent secretions, the use of the pus liquefying enzyme, Pancreatic Dornase, as a therapeutic adjuvant has proven helpful. The harmful potentialities of these secretions by obstructing airways and acting as a culture medium for infectious micro-organisms is recognizable. The rapid and safe evacuation of these secretions in the simplest possible manner is a problem of great importance.

Pressure Breathing Therapy.—Mechanical aids, such as the Vent-Elaire (Fig. 9), may be used for exsufflation with negative pressure (alternating positive-negative pressures). This technique is primarily employed for the removal of retained tracheobronchial secretions and uses the principle of a high positive pressure phase during inspiration with a rapid changeover to a high negative pressure phase during expiration.

A most valuable adjunct (at times life saving) in the therapy of patients with a complicating respiratory acidosis (Table III) is the use of an intermittent positive pressure on inspiration (IPPB/I) unit. With its use, the patient may be given higher concentrations of oxygen than usually considered advisable with relative safety. Aerosols (bronchodilator and detergolytic) should be simultaneously administered. Adequate alveolar ventilation is generally obtained with this technique. We have demonstrated improvement in the arterial oxygen saturation, reduction in arterial pCO_2 and return of pH to normal, in patients with alveolar hypoventilation secondary to chronic bronchial obstruction with this technique.

Aminophyllin.—Aminophyllin (theophyllin ethylenediamine) is a very useful drug in the management of progressive bronchospastic disease. As indicated in Table I, the methodology of aminophyllin administration depends essentially upon the severity of the patient's clinical bronchospastic state and aminophyllin tolerance. In the patient with mild chronic bronchial asthma, oral aminophyllin combined with anti-nausea factors such as the Cardalin or Dainite combinations, may prevent or minimize repeated bouts of bronchial asthma. High blood levels of aminophyllin without any considerable evidence of side reactions can be achieved by solutions of rectal aminophyllin and are indicated when bronchospasm is persistent. Aminophyllin suppositories are less reliable. In severe cases, the Dainite or Cardalin tablets may be used to supplement the rectal aminophyllin or to replace it when continued improvement has been noted.

However, during bouts of severe acute bronchospasm, it often becomes

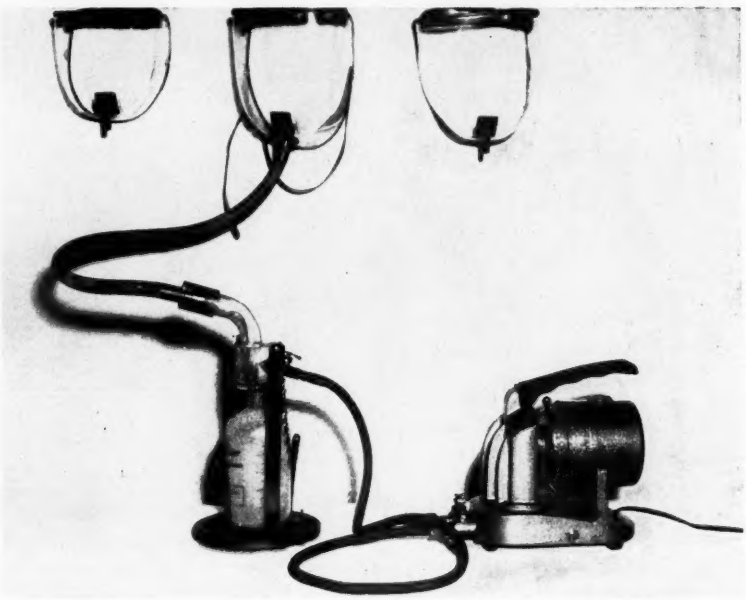

Fig. 7. Continuous aerosol technique with Eliot Air Pump—Neb-EL-izer—Face tent combination for: (a) water; (b) detergolytics, and (c) antibiotics.

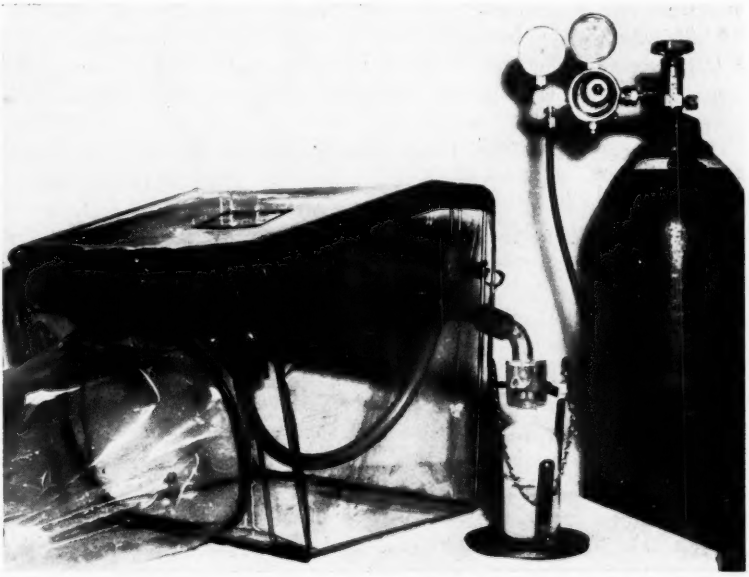

Fig. 8. O_2-Continuous aerosol technique (PermaTent Neb-EL-izer Combination). For O_2 with continuous aerosols of water, Alevaire, antimicrobials—"Croup Therapy."

Fig. 9. Multipurpose unit with various settings, for (1) Tracheal suction, (2) Intermittent therapeutic aerosols, (3) IPPB/I, (4) Exsufflation with negative pressure, (5) Alternating P & H pressure.

necessary, in conjunction with other forms of therapy, to administer aminophyllin directly by the intravenous route. When administered in this matter, aminophyllin *must* be given slowly to avoid any side effects. We generally administer 1 cc per minute of 0.5 gm aminophyllin in 20 cc solution.

For the patient in status asthmaticus, the continuous administration of aminophyllin by the intravenous route may be extremely beneficial, 0.25-0.5 gm of the drug is added to one liter of 5 per cent D/W and given at a flow rate of 30 drops per minute over a twenty-four-hour period. This should be continued for at least one day after all signs and symptoms of asthma have subsided. The indwelling plastic catheter-heparin technique may be necessary for long continuous use.

Steroid Therapy.—The earlier unbridled enthusiasm for the use of corticotropin and corticosteroids in the management of the patient with progressive bronchospastic disease has been replaced by a more cautious attitude based on experiences with a larger series of patients with various disease entities and with a wide variety of side-effects and toxic reactions (Table II). These hormones are essentially antiphlogistic agents with a capacity for increasing the resistance of cells in the inflammatory zone to the cytotoxic action of destructive agents. They apparently do not prevent

the formation of, or reduce, the inflammatory propensities of the toxic agents, *e.g.*, histamine. The physician pushing therapy may find himself like "the hunter holding the tiger's tail and afraid to let go" because of the problems attendant to withdrawal therapy.

TABLE IV. DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA
(Common Denominator: Cough—Wheeze—Dyspnea)

Intraluminal Obstruction	Extraluminal Obstruction	Miscellaneous
Neoplasm Benign Adenoma Papillomatosis Malignant Epidermoid Adenocarcinoma Undifferentiated Metastatic Infection Acute L-T-bronchitis bacterial-viral-chemical Chronic bronchitis Bronchiolitis Tuberculosis—endobronchial Foreign body Objects Erosion into bronchus (glands)	Neoplasm Teratoma Bronchogenic cyst Vascular Aneurysm of aorta Lymph nodes Lymphoma Metastases Tuberculosis Sarcoid Fungus Distortion of tracheo-bronchial tree Atelectasis (varied etiology) Pneumothorax Pneumoperitoneum Pleural effusion	Cardiac Acute L.V. failure Mitral stenosis L. atrial tumors Pulmonary "E-P syndromes" (Eosinophilic) (Pneumonopathy) Loeffler's syndrome Tropical eosinophilia Parasitic infiltrations P.E. infiltrations Malignant carcinoid (5-hydroxy-) (Indole A.A.) Chronic pulmonary emphysema with secondary bronchospasm

The specific physiologic and pharmacologic actions observed are related in degree to the basic chemical structure of different portions of the steroid employed. The salt retaining, carbohydrate and anti-inflammatory effects can be predicted from the basic structure of the steroid nucleus. In our clinic, the earlier cortisone and hydrocortisone preparations have been largely replaced by the newer prednisone, prednisolone, Meprolone® and Aristocort and Decadron preparations. An occasional patient may show considerable improvement with one of the earlier preparations when refractoriness to the newer corticoids occur. Psychic reactions and particularly anxiety and alertness noted in many on long term therapy may be prevented or minimized with Meprolone® (Prednisolone-Meprobamate). Patients with digestive complaints also appear to better tolerate this new combination. To minimize fluid retention and potassium loss, we have found the Pot-Amide preparation (0.5 gm Potassium Chloride and 0.5 gm Ammonium Chloride) very helpful. At present we are using Diuril in patients who show weight gain secondary to fluid retention and have been impressed with its ability to produce diuresis. With the attendant loss of sodium and chloride in the urine, we have not restricted these patients to a diet low in sodium and chloride.

More recently, we have been studying the usefulness of Aristocort (Triamcinolone Diacetate). This interesting new steroid analogue is very effective. In approximately two-thirds of our patients, a weight loss has been noted when changed from Prednisolone to Aristocort. On the other

hand, patients on the newer Decadron exhibit an increased appetite and real gain in weight, an advantage in the depleted, worn patient. To minimize adrenal suppression and atrophy in patients receiving long-term therapy with the corticoids, ACTH-Gel should be administered periodically, particularly when corticoid withdrawal is started.

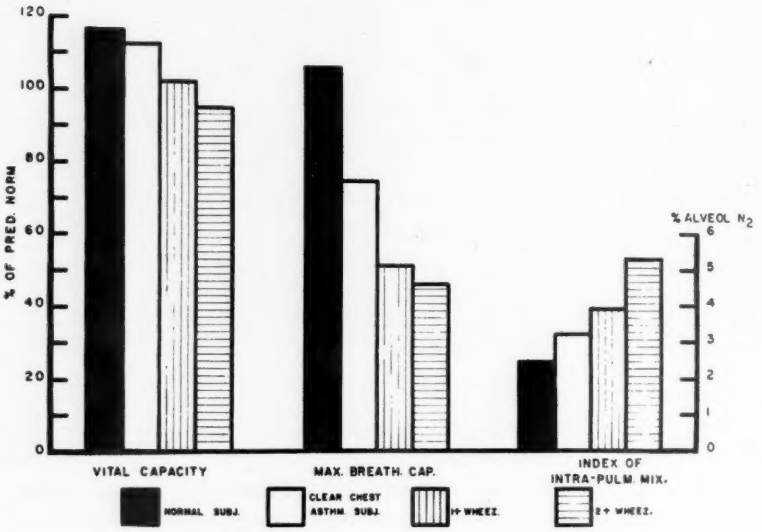

Fig. 10. Pulmonary functions according to lung findings.

3. PHYSIOLOGIC CHANGES AFTER THERAPY

In the evalution of the patient with the symptomatic wheeze, it must be borne in mind that many conditions other than asthma present wheezing as a prominent feature (Table IV).

Figure 10 correlates the severity of the wheeze with the vital capacity, maximum breathing capacity and index of intrapulmonary mixing. From this figure, the fact that the patients in the group without evident wheeze show a decreased vital capacity and maximum breathing capacity and an increase in the index of intrapulmonary mixing when compared with normal subjects is noteworthy. This difference becomes more evident as the degree of wheezing increases. Proportionate improvement may be anticipated with adequate therapy. The physiologic changes may be used as a guide for the success of the therapy employed, as well as the reversability of the disease.

From Figure 11 it will be seen that the patient with chronic bronchial asthma or pulmonary emphysema produces lower airflow rates, requires a

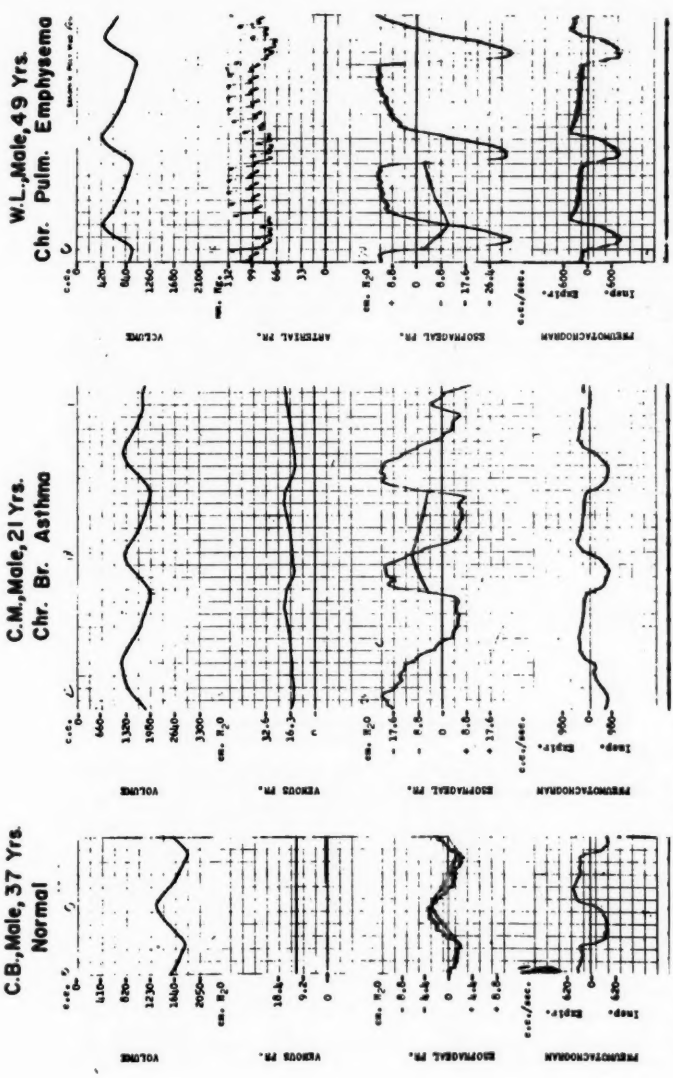

Fig. 11. Ventilatory dynamics in supine position during quiet breathing in a normal patient, a patient with chronic bronchial asthma during induced bronchoconstriction and a patient with severe chronic pulmonary emphysema.

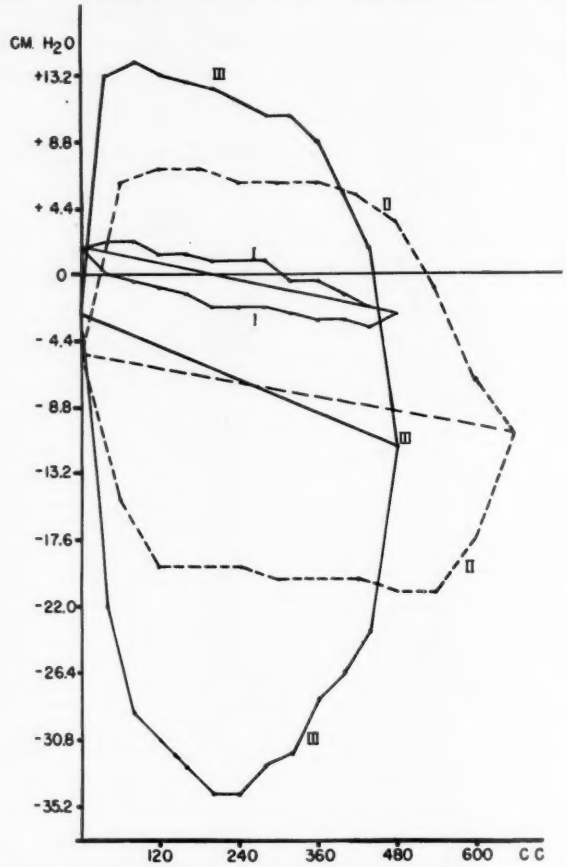

Fig. 12. Pressure-volume relationship during quiet breathing in a normal patient (I), in patient with C.B.A. during induced bronchoconstriction (II), and patient with longstanding, severe C.P.E. (III) (supine position).

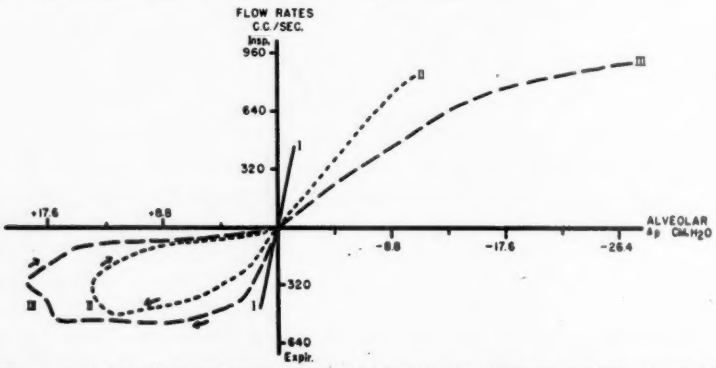

Fig. 13. Mechanical resistance-time relationship in different patients in supine position during quiet breathing: I—Normal; II—Chronic bronchial asthma; III—Chronic pulmonary emphysema.

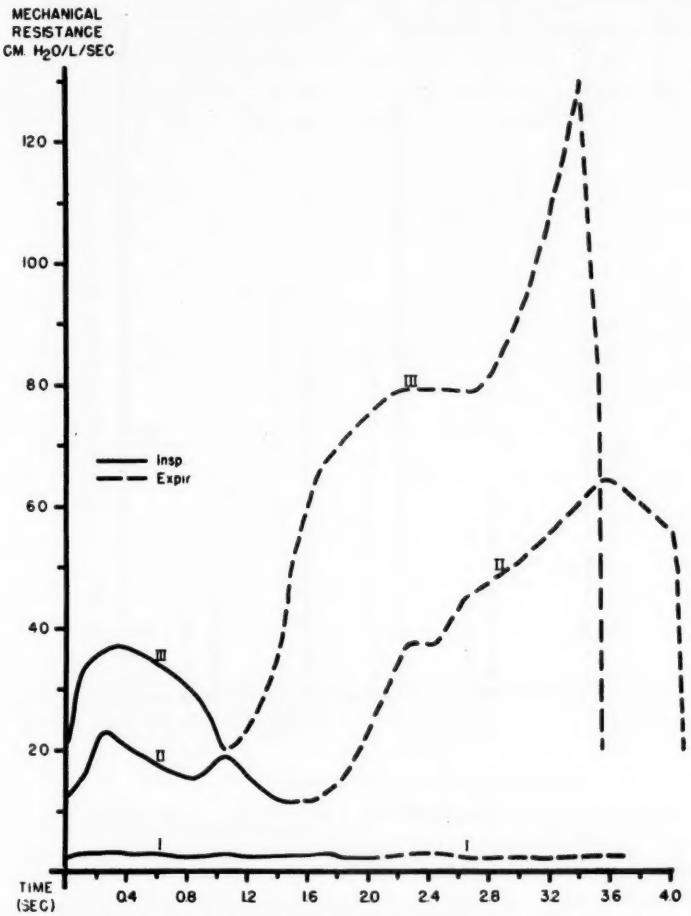

Fig. 14. Mechanical resistance during quiet breathing in normal patient (I); Patient with C.B.A. during induced bronchoconstriction (II); Patient with severe longstanding C.P.E. (III) (measurements in supine position).

greater pressure difference to move air in and out of the lung, and needs proportionally more time for expiration than the normal subject.

In Figure 12, the pressure-volume relationships in these three patients have been plotted from the data obtained in the recordings noted in Figure 11. The normal subject forms a narrow loop. The diagonal line represents the compliance, and forms a steep angle with the volume axis (normal compliance). It will be noted that the loops in the patients with chronic bronchial asthma and chronic pulmonary emphysema are much wider. This indicates that much of the work of breathing goes toward overcoming the mechanical resistance, and only a relatively small part toward overcoming

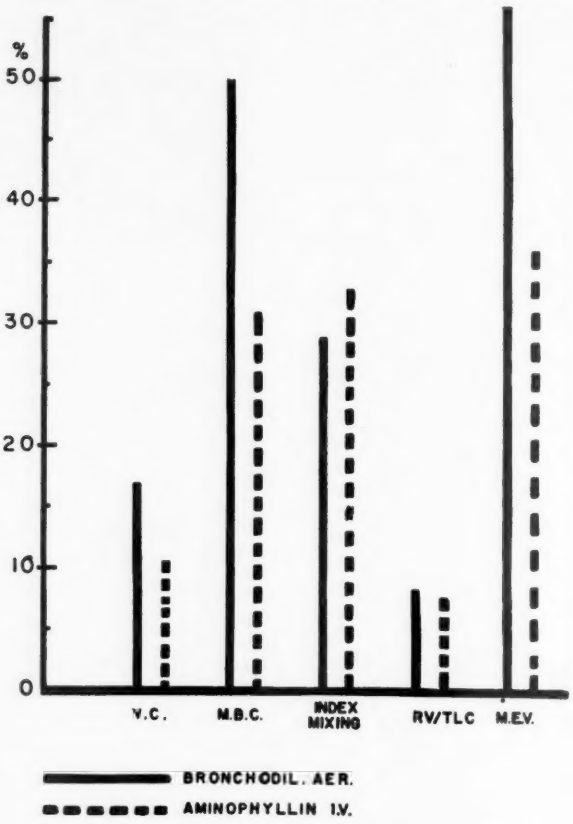

Fig. 15. Per cent improvement after treatment. Summary.

TABLE V. TREATMENT OF RESPIRATORY ACIDOSIS*

1. *Preventive (Best Treatment)*
   (a) Early recognition of signs and symptoms
   (b) Avoid high concentrations of oxygen
   (c) Avoid respiratory depressing drugs
   (d) Avoid combination of (b) and (c)
   (e) Vigorous antimicrobial therapy
2. *Etiologic*
   (a) Drug intoxication
   Opiates—N-allynormorphine
   Barbiturates—picrotoxin
   (b) Acute obstruction of airways
   Bronchoscopy
   Tracheotomy
3. *Symptomatic*
   (a) IPPB/I-Bennett unit
   (b) Mechanical respirator chambers (Emerson-Drinker units)
   (c) Emergency pneumoperitoneum
   (d) Graded program of oxygen therapy
   (e) Etiologic treatments when indicated

*From Chronic Pulmonary Emphysema. Physiopathology and Treatment by M. S. Segal and M. J. Dulfano. Courtesy of Grune & Stratton, Inc., New York, 1953.

the elastic forces of the lung. Furthermore, the elastic recoil of the lung is insufficient to perform the expiration. The increased resistance has to be overcome by an active effort of the expiratory muscles.

In Figure 13, the resistive pressures (X axis) have been plotted against the flow rates (Y axis). The curves represent the mechanical resistance

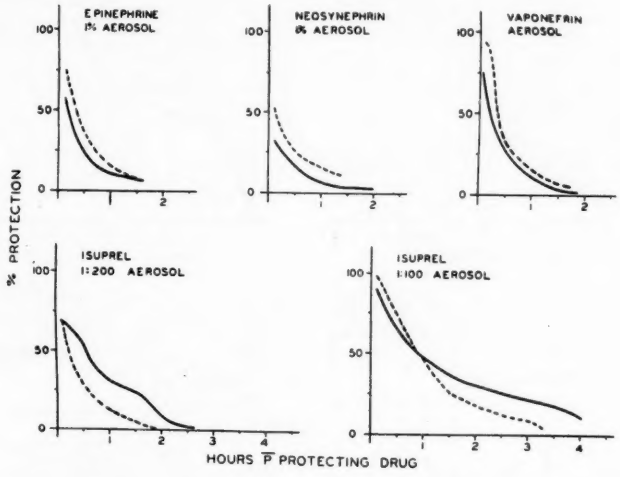

Fig. 16. The protecting action of adrenergic agents administered by the aerosol route against the dyspnea and bronchospasm produced by histamine and methacholine. Epinephrine, 5 trials; Neosynephrin, 4 trials; Vaponefrin, 5 trials; Isuprel—both dilutions, 6 trials. The dotted line indicates histamine and the solid line indicates mecholyl.

obtained in these three individuals. The two patients show a marked increase in resistance during both inspiration and expiration. The expiratory tracing shows a loop instead of a single line as noted in the normal subject. The pressure necessary to obtain a given flow rate increases progressively during the expiratory cycle. Part of this is caused by the progressive narrowing of the tracheobronchial tree as deflation goes on. Another part might be the result of expiratory ball-valving.

In Figure 14, mechanical resistance has been plotted against time in the three individuals. The normal subject shows about the same resistance during the whole cycle, while both patients show a marked increase during inspiration and a tremendous increase during expiration. These studies (Figs. 11-14) clearly demonstrate why patients with chronic bronchial asthma or chronic pulmonary emphysema may be fully incapacitated, despite little radiologic or pathologic evidence of disability. A large part of their energy and their oxygen uptake is spent on the breathing process alone. A reduction in the respiratory work, either by mechanical ventilatory aids or by bronchodilator drugs, improves the pulmonary gas ex-

change, making more oxygen available for non-respiratory metabolic needs of the body.

Table V gives a comparison of the mean values for various pulmonary

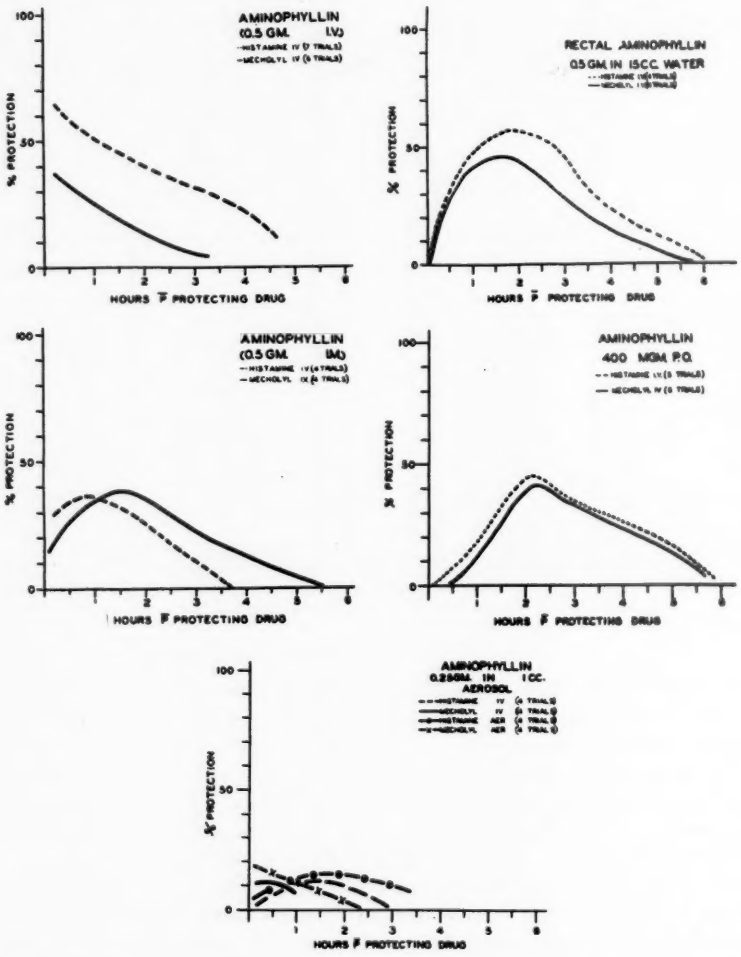

Fig. 17. The protecting action of aminophyllin administered by various routes against the dyspnea and bronchospasm produced by histamine and methacholine.

physiological studies of patients with bronchial asthma and the normal group; the pulmonary compliance is low and falls even further during rapid breathing. The mechanical resistances during both inspiration and

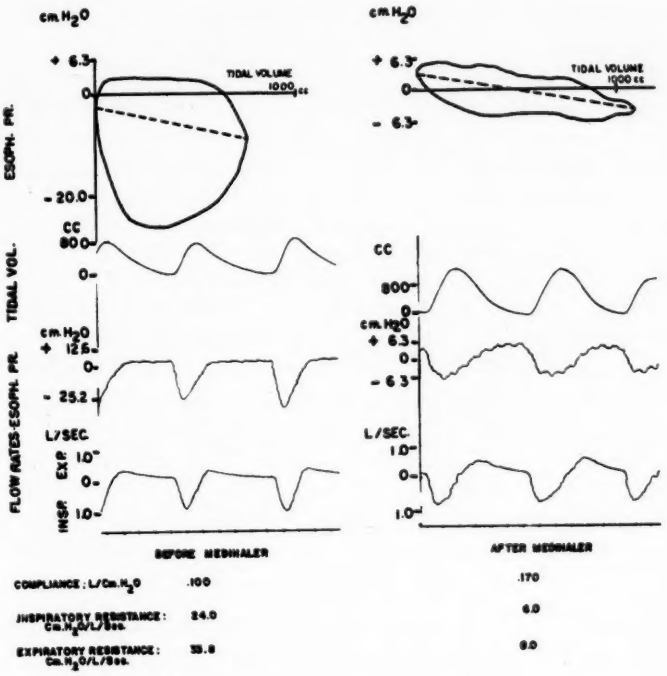

Fig. 18. Mechanics of breathing in a patient with chronic bronchial asthma (H.P., man, aged forty-four) before and after Medihaler isoproterenol inhalations × 6.

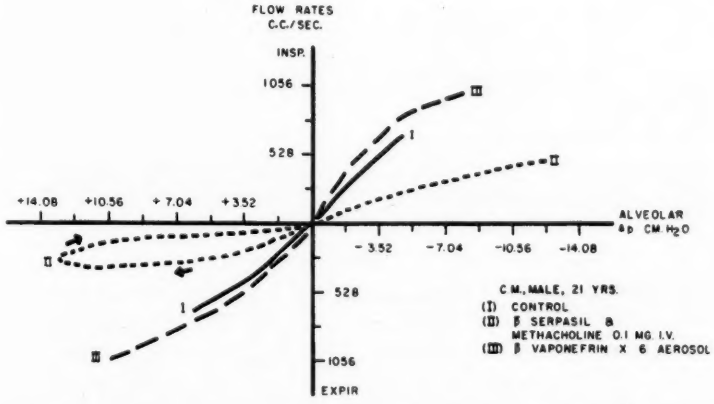

Fig. 19. Changes of mechanical resistance in a patient with chronic bronchial asthma (I) at rest, (II) during induced bronchoconstriction and (III) after bronchodilator aerosol (supine position).

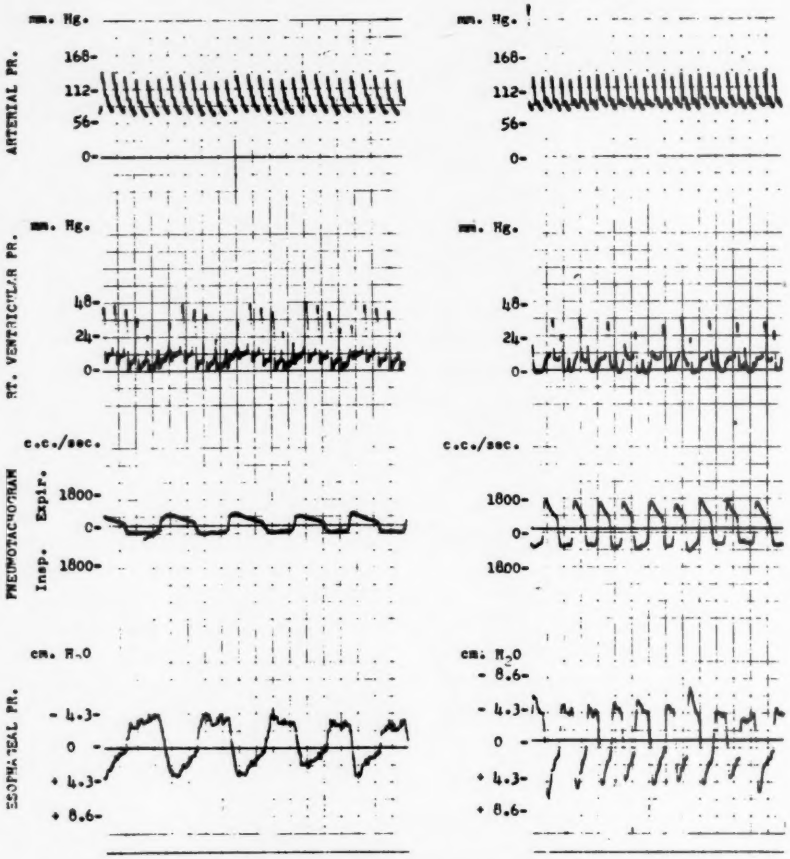

Fig. 20. Ventilatory and circulatory dynamics in a patient with chronic pulmonary emphysema before and after 0.5 gm. of Aminophyllin (I.V.). (Patient J. C., man, aged thirty-nine).

expiration are markedly increased as compared with the mean values for the normal subjects.

4. RESULTS

Figure 15 graphically summarizes the percentage of improvement in various pulmonary function studies and lung volumes following the administration of both bronchodilator aerosols and intravenous aminophyllin. Improvement with the bronchodilator aerosols was noted within five to ten minutes, and with intravenous aminophylline, within ten to twenty minutes. Duration of improvement varied from thirty minutes to six hours, depending upon the degree of bronchospasm. The most outstanding

improvement following therapy in these patients with bronchospastic disease is noted in the MBC and MEV. This is probably indicative of a decrease in the bronchospastic state and lessening of the airway resistance.

Figures 16 and 17 summarize the results of the protecting action of adrenergic aerosol preparations and aminophyllin by various routes against the bronchospastic crisis induced by the intravenous administration of histamine and methacholine. In the adrenergic aerosol protecting group, Racemic epinephrine and isoproterenol appear to have the greatest protecting actions. In the aminophyllin study, the use of the aerosol route appears to offer little beneficial protecting action against the bronchospasm induced by histamine or methacholine. As is the case with clinical trials with aminophyllin, the use of the drug by the intravenous, rectal and oral routes in that order are most advantageous.

Figure 18 demonstrates the pressure-volume relationships derived from the original tracings of patient H.P. before and after therapy with the Medihaler-Isoproterenol (alcoholic). The left hand portion of the figure represents the pre-treatment control. On the right, the post-treatment results are shown. The original tracings are noted in the lower part of the figure; the loops representing the pressure-volume relationships are located in the upper section. The pressure-volume loop on the left is wide, and the compliance is low (0.10). The wide loop is indicative of an increased resistance to the movement of air in and out of the lungs and an elevated work of breathing. This is of particular significance during expiration where active work is required rather than dependence upon the elastic recoil of the lungs. Following therapy with the Medihaler-Isoproterenol (alcoholic), the compliance rises, and the loop narrows. Thus, with the relief of bronchospasm, the work required to move air in and out of the lungs lessened.

Figure 19, by plotting resistive pressures against flow, a curve is obtained which represents the mechanical resistance. By inducing bronchospasm with the intravenous administration of methacholine, increased mechanical resistance results (II.). Examination of the plotted line obtained following bronchospasm reveals a loop in expiration which is presumably the result of "ball-valving." The post aerosol line indicates a reversal of bronchospasm with a decrease in the mechanical resistance.

Figure 20 shows that following the intravenous administration of aminophyllin to a patient with chronic pulmonary emphysema and evidence of bronchospasm, the flow rates increase to almost twice the control level without a corresponding increase in transpulmonary pressures. While peripheral arterial pressure remains essentially unaltered, there is a drop in right ventricular pressure. In the presence of an increased cardiac output, this is indicative of a lowering in pulmonary vascular resistance.

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Submitted June 12, 1958

A GRAPHIC FORM AS A PROGRESS INDEX OF ASTHMATIC PATIENTS

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ASTHMA is neither a self-limited illness, nor is it characterized by uniform progression of severity. Rather, the syndrome of asthma is marked by episodic attacks of acute illness of variable degree interspersed with periods of freedom from disability. In such a setting it is extremely difficult to ascertain etiologic relation between every life event and the onset of the attack. Furthermore, the nature of the disease is such as to require that some graphic method be developed which might afford opportunity for recording, as objectively as possible, the events in the life of an asthmatic patient which might have relevance to the initiation or amelioration of an attack. In short, any understanding of the life history of the disease could profit by creating a graphic method for recording it.

The problem of evaluating all the variables chronologically related to an asthmatic episode is as important in private practice as in an institutional setting.

The Jewish National Home for Asthmatic Children at Denver provides facilities for the care of 150 intractably asthmatic children, ranging in age from five to fifteen years.[1-3] The children are housed in six separate cottages and the average residence is eighteen to twenty-four months. Patients are seen by a physician for a regular general examination as often as illness demands but at least once a month for every patient. The children visit the institution's dispensary, either on their own initiative, or on referral by their houseparent whenever there is any need for medical attention. The children are instructed in the use of a nebulizer, and an attending nurse prepares one for use as needed (isoproterenol hydrochloride solution with compressed air). Any child who has required nebulization therapy several (three to five) times during a twenty-four-hour period is referred for an examination to the attending physician and further management is prescribed as indicated.

The detailed evaluation of this remarkable population of children has been facilitated by the construction of a graphic form which is incorporated in the patients' records. The accumulating sheets can also be used after the child is discharged, as a quick reference to the case and as a practical means of collecting statistical data. It should be emphasized that this chart is used as a supplement to and not a substitute for the regular patient records.

Recent studies[4,5] have attempted to grade the severity of symptoms re-

From the Jewish National Home for Asthmatic Children (J.N.H.A.C.) at Denver, Colorado.

ported by the patient or his parents with objective tests and with the amount of medication required for relief. In the institutional setting of the Home four factors have been taken into account in assessing the severity of illness in each patient during a given time interval: (1) the number of visits to the dispensary for relief of acute wheezing by nebulizations, (2) the frequency and duration of hospitalizations for asthma (marked on the graph by XX), (3) measurements of pulmonary function, and (4) the kind and amount of medication used for the control of asthma. The graphic form described in the present communication was not designed to record the diet since this is entered in the regular patient record. Rather, the object of the graphic form is to provide an over-all progress record covering a period of six months on a single sheet.

Certain limitations were unavoidable in designing the form; for example, a weekly record does not show whether the number of nebulizations recorded was required in a one, two or seven-day span. Children differ in their degree of apprehensiveness concerning their asthma. Some will want to use a nebulizer for relatively mild wheezing, while others will ignore considerable respiratory discomfort in order not to interrupt more pleasurable activities. Yet, after a certain period of residency at the Home, some degree of uniformity of reactions is acquired. Information pertaining to a child's behavior, reaction patterns, interpersonal relations, or any significant changes in his environment, such as visits, change of room or building, is difficult to relate graphically to the pattern of asthma, but the attempt is made by recording it at the bottom of the sheet (counseling).

Pulmonary function tests are performed regularly on all patients at intervals ranging from one to six months, and in special instances, are repeated daily or weekly. These include vital capacity, one-second vital capacity and maximum breathing capacity before, as well as after, nebulization with isoproterenol hydrochloride solution. For the purposes of the graph, only vital capacity before nebulization has been recorded. Monthly measurements of height and weight of the patients are also included.

The amount of corticosteroids and ACTH administered is graphically represented in a separate section. As of December, 1957, 21 per cent of the population was on maintenance steroid hormones,[3] prednisolone being the drug most often used. Other preparations, however, like intravenous hydrocortisone succinate, ACTH, or the newer steroid hormone compounds, have been used and are appropriately recorded. Different colors have been used for the sake of clarity and readability. Other drugs are represented by initials, and a code at the bottom of the sheet offers an explanation for the symbols used. A continuous line indicates the period of time the patient has been on any particular medication.

Hyposensitization injections are marked by circles, crosses or other signs. The dosage and concentrations are not stated, this information being easily obtainable from each child's special therapy sheet.

It was thought that a few examples of the form in use may make its

practical application more evident. Five patients have been chosen, selection being intended to show the variety of factors operating in each patient. Problems of pollinosis, food sensitivity, infectious and psychophysiologic components, are all graphically represented in Figures 1 to 5. Each patient history is briefly summarized to elucidate certain points. The selected patients are not representative of the general population of the Home.

CASE REPORTS

Case 1.—D. M., a fourteen-year-old boy from Denver, Colorado, has a history of asthma dating from early infancy. He was first seen by his referring physician in August 1954. At that time, he was staying with his grandmother due to friction with his father. There was a report of seasonal aggravation of symptoms in April and May 1954, and again in the late summer. Injection therapy was given sporadically in 1955, and again resumed in late March 1956. After a period of no contact, the family again visited the referring physician shortly before admission. By then, D. M. required large doses of cortisone and ACTH for control. He was admitted to the Home on June 24, 1957. The graph shows the very marked asthma during the summer (thirty-five nebulizations during the last week of July), clearing in October and November. It should be noted that this boy was ill with Asian influenza during the last week of September.[3] Skin tests were positive for grasses, ragweed, Alternaria, Helminthosporium and Aspergillus. There was a recrudescence of asthmatic symptoms in December which may have been due to a mild respiratory infection. At the time of this writing (February 1958) he is on weekly injections of grass, weed and mold extracts.

Case 2.—E. K., a boy, aged twelve, from Cincinnati, Ohio, began to have asthma at four years of age with severe attacks throughout the year, the interval between attacks never being more than two weeks. Since his admission on August 1, 1956, he has enjoyed absolute freedom from asthma for periods of from one to two months. When he did have some wheezing, no more than three nebulizations per week were needed with ensuing prompt relief. Skin tests were strongly positive for molds, grasses and weeds and appropriate injection therapy was begun in May 1957. A severe episode of wheezing occurred in June 1957, coincident with his parents' visit. This was followed by continuing asthma during July and August. He then remained perfectly free from asthma from the end of September until December when asthma recurred coincident with his parents' return. The asthma, however, lasted only four days, and his symptoms disappeared even before the mother's departure. He, as did the patient in Case 1, became ill with Asian influenza the last week of September, 1957.

Case 3.—S. V., a girl, aged eight, from Cleveland, Ohio, was admitted on August 10, 1957. At that time, she was on 10 mg prednisolone daily and had been on steroid hormones for the preceding five years. Asthma first appeared at one and one-half years of age and showed no seasonal variation except for possible aggravation by colds. Eczema*, still present in mild form, had been worse in the summer. The patient has been treated with spring, summer and fall pollens but since admission she has suffered four major asthmatic episodes, all associated with signs of upper respiratory infection. To date, attempts to reduce her dosage of steroid hormones have been unsuccessful.

*A modification of the graph is used for the follow-up of cases of eczema, focus being placed on the dermatologic problems and asthma tracings recorded underneath, for comparison.

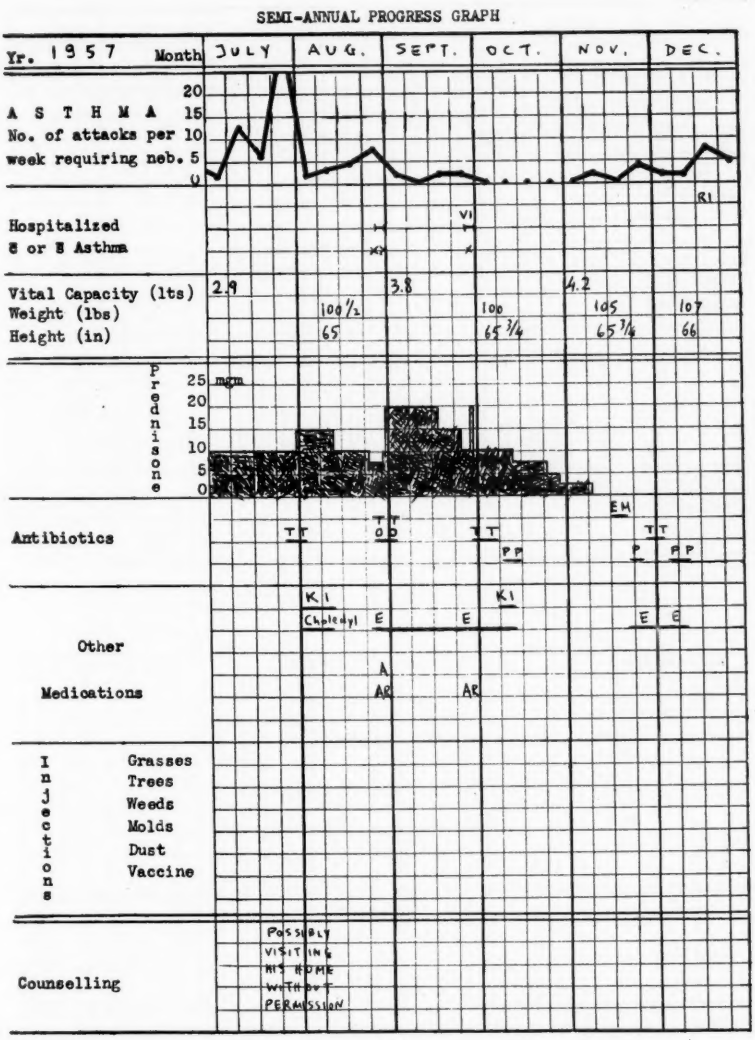

Fig. 1. Case 1 (D. M.), aged fourteen, admitted June 24, 1957, from Colorado.

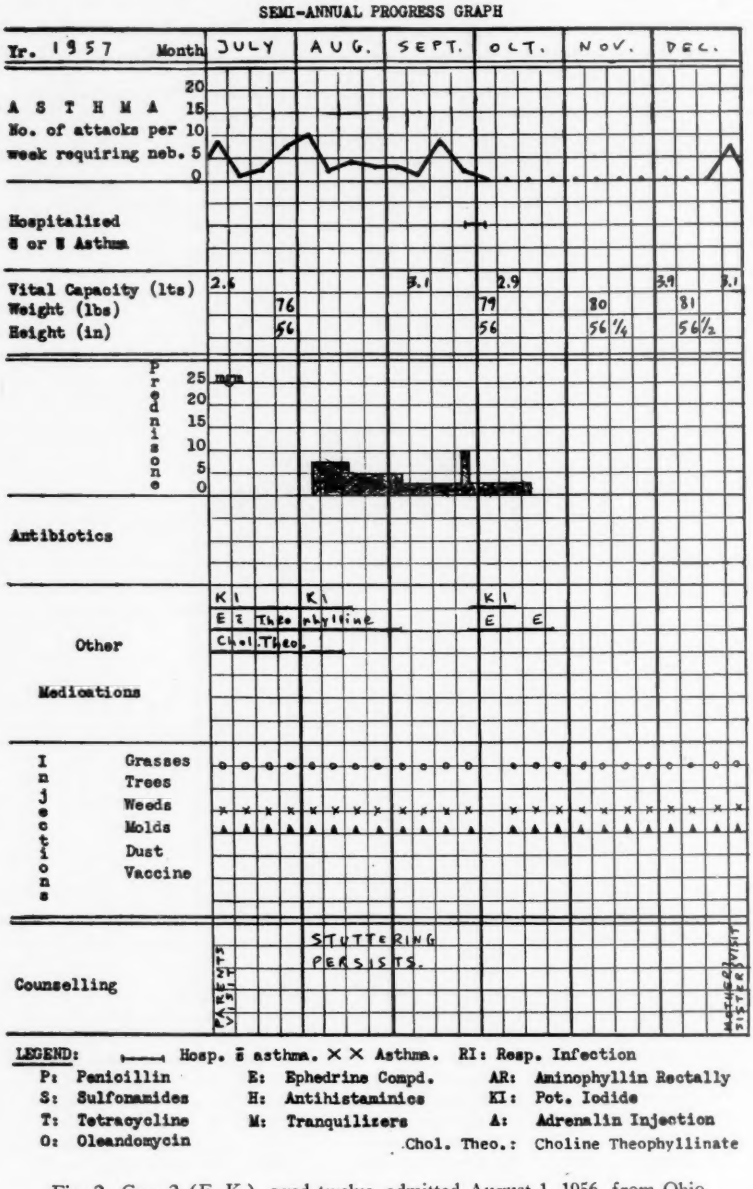

Fig. 2. Case 2 (E. K.), aged twelve, admitted August 1, 1956, from Ohio.

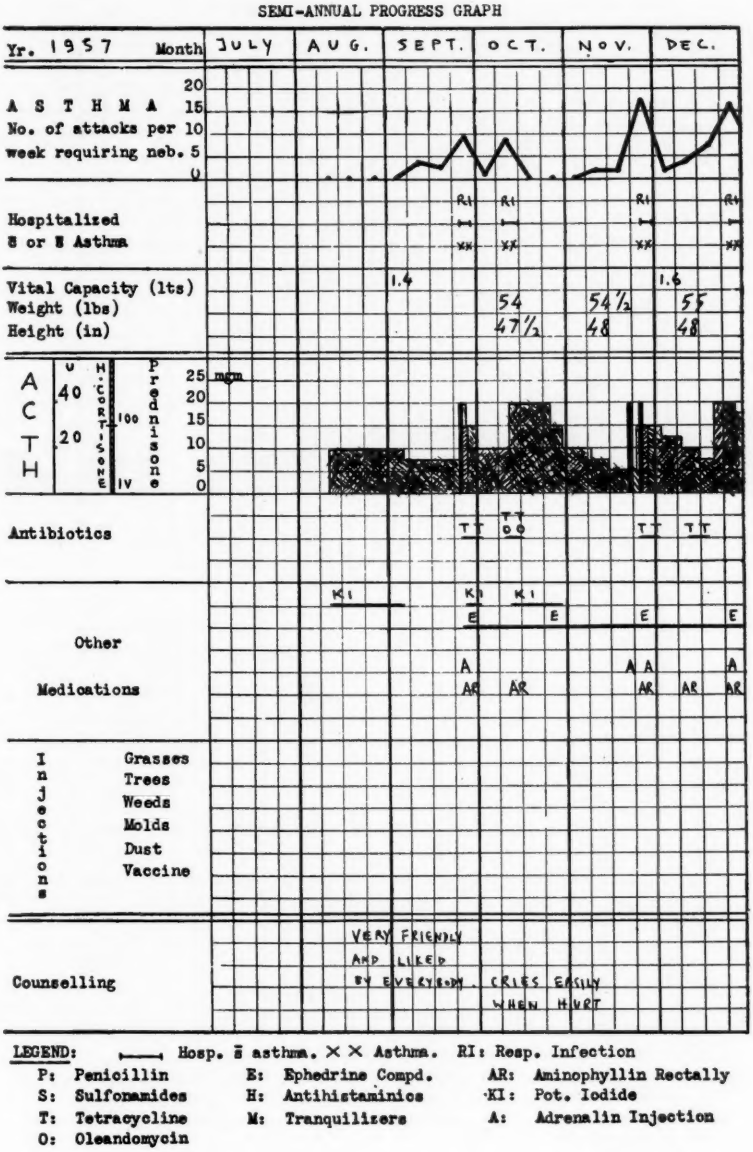

Fig. 3. Case 3 (S. V.), aged eight, admitted August 10, 1957, from Ohio.

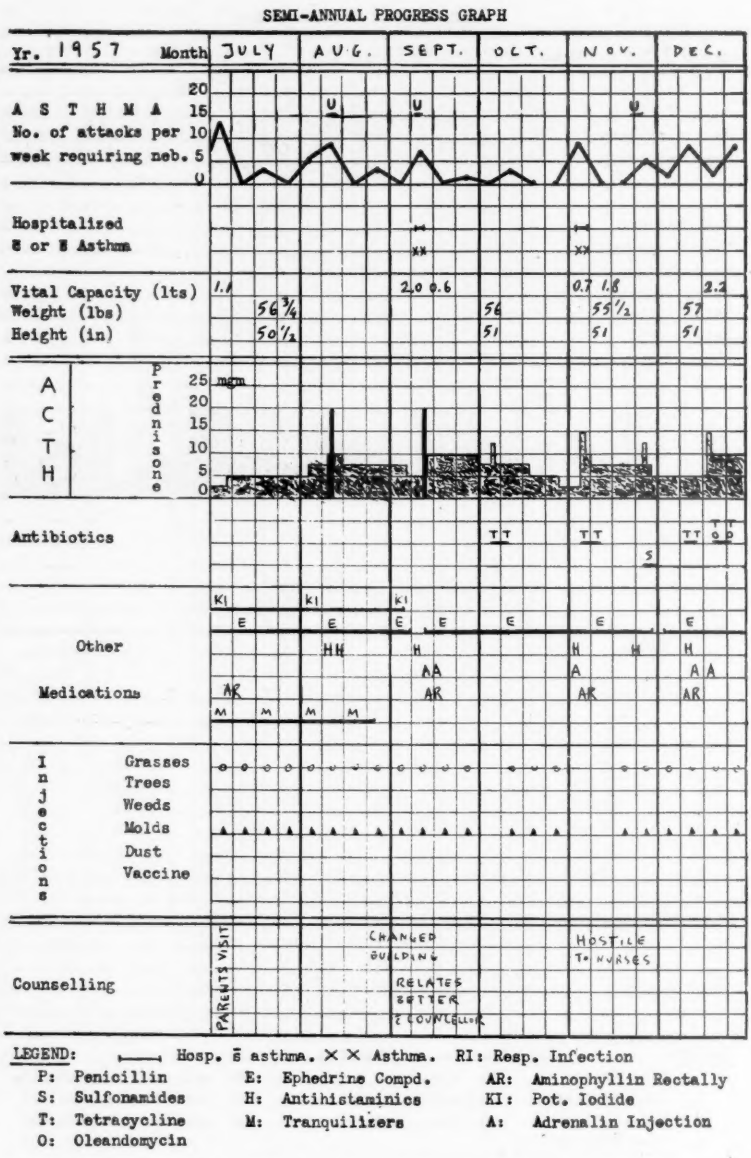

Fig. 4. Case 4 (R. P.), aged eight, admitted November 6, 1956, from New York.

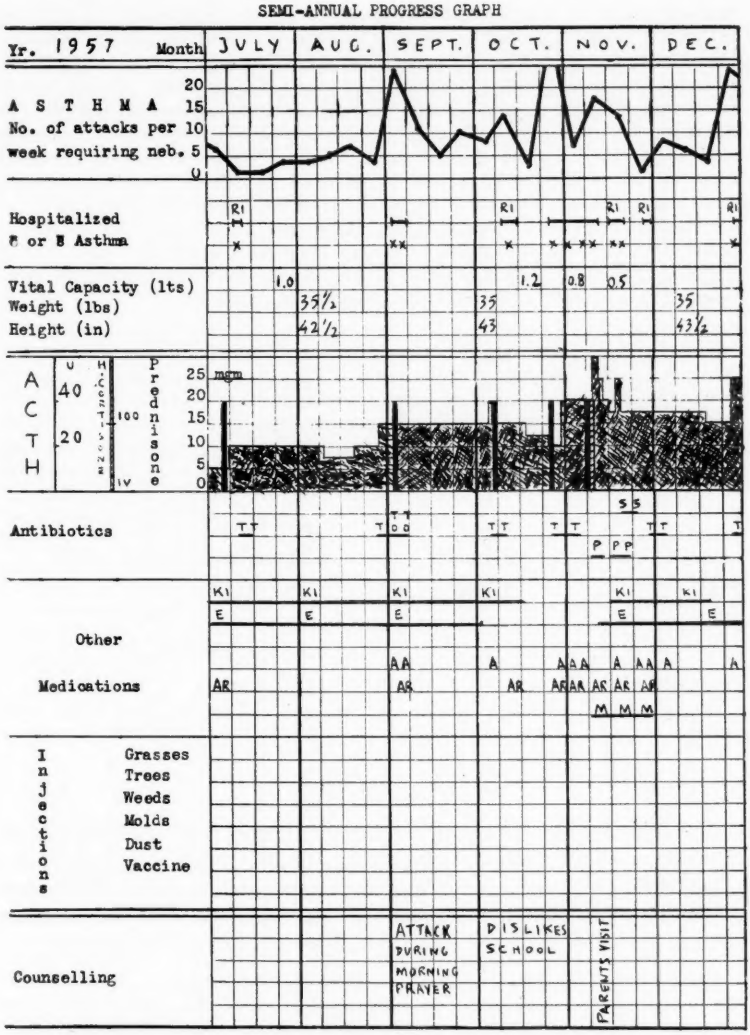

Fig. 5. Case 5 (T. L.), aged six, admitted February 21, 1957, from California.

Case 4.—R. P., a boy, aged eight, who came to us from New York, is reported to have begun having asthma at nine months of age, with eczema preceding it. There had been two to three mild attacks per month during the period preceding admission and he was receiving prednisone, 20 mg a day, for control of his asthma. Following admission November 6, 1956, the patient continued to have two to three mild attacks of asthma per month, seldom requiring more than five nebulizations a week. By the end of 1956, the dosage of prednisolone was reduced to two and one-half mg daily. On skin tests, there was shown a marked reaction to molds and weeds. R. P. has been receiving weekly injections of grass and mold extracts since May 1956. The graph shows the relatively mild, but persistent, nature of his asthma. Events of everyday life, such as minor frustrations, anger, over-exertion, often seem able to elicit an acute asthmatic attack. On one occasion in 1956, and three times in 1957 (shown on graph) he had urticarial reactions with some angioedema of the lips due to the ingestion of certain food items to which he was skin-sensitive. An aggravation of his asthma following each of these episodes can be seen on Figure 4.

Case 5.—T. L., a six-year-old boy from San Diego, California, was admitted February 21, 1957. Asthma, first diagnosed at thirteen months of age, was reported to have been continuous, mild or severe and aggravated by infections, excitement, emotions or wind. He had been on cortisone since 1953, and just prior to admission, was taking prednisone, 5-20 mg daily. Epinephrine had to be used quite frequently. The referring physician described the rapid subsidence of an acute attack following the injection of sterile water, the patient believing he was getting epinephrine. A similar experience followed his arrival in Denver, an acute asthmatic attack disappearing promptly after either an injection of isotonic saline or soon after admission to the hospital. His attacks have no definite pattern whatsoever and often would occur rapidly for no apparent reason, or on other occasions after being disciplined or after an upper respiratory infection. On October 11, there was roentgenographic evidence of paratracheal adenopathy with atelectasis, associated with an upper respiratory infection and asthma (para-asthma).[6] This showed complete clearing in subsequent films. The pattern of asthmatic attacks, however, continued unchanged.

The visit of his parents in October was the result and not the cause of his severe asthma.

SUMMARY

A graphic form is described for the recording of pertinent data relating to the occurrence of asthma in the patients residing in an institution for the rehabilitation of intractable asthma in children (J.N.H.A.C.). Each page of the form summarizes six months of the life history of the asthmatic child in a manner facilitating the evaluation of the individual patient.

Five cases from the J.N.H.A.C.'s present population are presented for the purpose of rendering the practical application of the above form more evident. The patients (not representative of the total population) were selected to demonstrate pollen asthma as well as food sensitivity with urticaria, and infectious and psychophysiologic problems.

REFERENCES

1. Peshkin, M. M., and Tuft, H. S.: Rehabilitation of the intractable asthmatic child by the institutional approach. Quart. Rev. Pediat., 11:1 (Feb.) 1956.
2. Tuft, H. S.: The development and management of intractable asthma in childhood. A.M.A. Am. J. Dis. Child., 93:251-54 (March) 1957.

3. Falliers, C. J., Bekaroglu, M., and Peshkin, M. M.: Observations on children with intractable bronchial asthma in an institution during a viral epidemic. To be published.
4. Lowell, F. C., Schiller, I. W., and Lynch, M. T.: Estimation of daily changes in the severity of bronchial asthma. J. Allergy, 26:113-121 (March) 1955.
5. Johnstone, D. E.: Study of the role of antigen dosage in the treatment of pollinosis and pollen asthma. A.M.A. Am. J. Dis. Child., 94:1, 1957.
6. Peshkin, M. M.: Allergy in children. *In* Progress in Allergy, Vol. III. Ed. by Paul Kallos. New York: Interscience Publishers, Inc., 1952.

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Submitted May 12, 1958

AUTHOR'S CHOICE

Under what circumstances should the traditional customs of scientific publication be followed, and under what circumstances is it preferable to give a scientific report to the public press prior to its appearance in a scientific journal? The research worker has a choice. If he presents his material in an open meeting or gives it directly to the press, newspapers can report it immediately. The material reaches the public quickly—if at all—but relatively unscreened and rarely in sufficient detail to enable other scientists to form their own judgments about the adequacy of the conclusions.

If the report is published in a scientific journal, it does not reach the public as quickly, but when it does, it has survived critical scientific review, has frequently been made clearer as a result of suggestions from the editor or referee, and is published in sufficient detail to enable scientific colleagues to appraise data and methods as well as conclusions.

Custom dictates that the choice be made by the scientist rather than by the institution that supported the work or the editor to whom the account of it is submitted. Both alternatives have their proper uses, but there is not yet agreement on the conditions under which each is preferable. Until agreement is reached on the criteria for each, we will honor the choice an author makes when he sends an article to Science. We will continue to have articles critically reviewed and will publish the accepted ones in sufficient detail to enable other scientists to gain more information than they can normally get from newspaper accounts. Note, however, that when an author wishes to reach the public more quickly, there is an alternative channel open to him.

We think it desirable that both scientists and journalists have a clear understanding of the nature of these options.—D. W., Editorial, *Science*, 129:1247 (May 8), 1959.

STUDIES ON THE NEUTRALIZING AND ELICITING ACTIVITY OF ALTERED RAGWEED ANTIGEN

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THE possibility of application of experimental knowledge regarding hapten immunochemistry to clinical pollenosis has not received extensive investigation. Landsteiner's work on sensitization to hapten-protein complexes demonstrated that the hapten alone was capable of inhibiting the precipitin reaction between certain hapten-proteins and antisera.[1] He also showed inhibition of anaphylaxis by preliminary injection of hapten into guinea pigs sensitized to hapten-protein complexes.[2] Heidelberger and Kendall[3] observed that partial hydrolysis products of specific polysaccharide of the pneumococcus could inhibit precipitation with homologous rabbit antisera. Tillet, Avery and Goebel[4] also showed hapten inhibition of anaphylaxis in guinea pigs. They sensitized guinea pigs to carbohydrate-protein complexes capable of producing anaphylaxis when the whole complex was used to challenge the pigs. When the glucoside alone was used, specific desensitization for short periods was produced.

It was proposed by one of us (K.P.M.) that if ragweed hapten existed as such or could be produced by alteration of ragweed extracts, such a hapten could possibly neutralize reagin in the ragweed sensitive patient without the release of histamine or histamine-like substances. The possibility of the existence of such a hapten was suggested by the work of Benjamins, Von Dishoeck and German,[5] who reported that ultrafiltrates of ragweed extracts contained low molecular weight substances which were "activated" by large protein molecules. Long and Teller reported similar results.[6] Service[7] stated that polysaccharides obtained from pollens would inhibit anaphylactic or Dale reactions in guinea pigs if they were administered prior to the pollen antigen.

Hapten in ragweed extract might exist as a free carbohydrate substance, a free polypeptide, or as a carbohydrate or polypeptide group attached to a larger protein molecule. The extensive investigation on ragweed antigens conducted in several laboratories[8-17] have demonstrated skin reactivity in fractions of extracts obtained by several different chemical procedures. These results could be explained in part by the presence of a single or limited number of different haptenic groupings on protein molecules widely variant in

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Mr. Correa's work was supported by an undergraduate scholarship award from the Allergy Foundation of America.

size. Some substantiation of this concept is offered by the work of Pringle,[8] whose data suggested the presence of a very limited number of terminal amino acid residues, if any at all, in crude ragweed extract. For this investigation, crude ragweed extracts were chosen without attempting to purify the material physically or chemically. If hapten exists as a free carbohydrate or polypeptide material of low molecular weight, dialysis through a cellophane membrane should separate a majority of it from larger molecules. If it is attached to a larger protein molecule, its separation might be possible by hydrolysis under varying chemical or physical conditions such as proteolytic digestion, acid hydrolysis, heat, or combinations of the above methods.

Such a hapten could theoretically be demonstrated by a modification of the passive transfer neutralization reaction. This method, based on the work of Cooke and his associates[18] and Stull and Sherman[19] and critically evaluated by Arbesman and Eagle,[20] is one of the most reliable methods presently available for assaying allergens. Ragweed extract in sufficient amount will neutralize the ragweed reagin in serum from a sensitive individual. This mixture, injected into the skin of a non-sensitive recipient, will not result in a skin reaction when challenged with ragweed extract twenty-four hours later.[20] Serial dilutions of ragweed extract added to aliquots of serum from a ragweed sensitive individual, planted intradermally in a non-sensitive recipient and challenged with ragweed extract will give a measure of the extract's neutralizing ability and thus its antigen content.

The presence of haptens capable of neutralizing reagin without the release of histamine or histamine-like substances might be demonstrated in the following manner. The neutralizing capacity of a ragweed extract is determined as described. The eliciting ability of the same ragweed extract is also obtained by challenging passive transfer sites sensitized by the same reagin-containing serum with serial dilutions of the ragweed extract. If material containing ragweed hapten is added to the ragweed extract and the above passive transfer neutralization and elicitation reactions repeated, the results should show a relatively greater increment of neutralizing ability than eliciting ability. Thus the test is designed to identify the presence of haptenic substance by its ability to alter the neutralizing: eliciting ratio of ragweed extract. Accordingly, various hydrolysates of ragweed extract were tested in this manner to determine whether haptenic activity was present. An attempt was made to hydrolyze them to a degree which produced some, but not complete, loss of skin eliciting ability.

EXPERIMENTAL METHOD

Preparation of ragweed extract.—A 1:50 solution of ragweed extract was prepared by extraction of Ambrosia elatior with buffered saline in the usual manner[21]; 1 ml of the 1:50 ragweed extract contained .35 mg of nitrogen as determined by the Kjeldahl method.

Acid hydrolysis.—10 N hydrochloric acid. Concentrated hydrochloric acid was added to 1:50 ragweed extract to prepare a solution with a final concentration of 10 N HCl. Aliquots of this solution were hydrolyzed at 37° C for periods of five, ten and twenty-four days, and evaporated to

TABLE I. TECHNIQUE OF DETERMINING THE ABILITY OF AN ALTERED RAGWEED EXTRACT TO CHANGE THE NEUTRALIZING:ELICITING RATIO OF A CONTROL RAGWEED EXTRACT

Day One			
Neutralizing		Eliciting	
Control	Altered Extract	Control	Altered Extract
Plant P.K. sites with mixture of equal amounts of: 1. Reagin serum. 2. Serial four-fold dilutions of ragweed extract. 3. Buffered saline.	Plant P.K sites with mixture of equal amounts of: 1. Reagin serum. 2. Serial four-fold dilutions of ragweed extract. 3. Altered extract.	Plant P.K. sites with reagin serum	Plant P.K. sites with reagin serum
Day Two			
Control	Altered Extract	Control	Altered Extract
Challenge all sites with ragweed extract	Challenge all sites with ragweed extract	Challenge all sites with mixture of equal amounts of serial four-fold dilutions of ragweed extract and buffered saline.	Challenge all sites with mixture of equal amounts of serial four-fold dilutions of ragweed extract and altered extract.

dryness to remove the hydrochloric acid and the residue dissolved in distilled water to approximate the original concentration of 1:50. This extract was dialyzed against buffered saline, and the dialysates and dialysate residues were tested for eliciting and neutralizing activity on Prausnitz-Kustner sites. Neither eliciting nor neutralizing ability remained, and these hydrolysates were discarded.

Next, acid hydrolysis was conducted in the same manner at concentrations of 3 N, 1 N and .1 N for varying periods of time. At completion of hydrolysis, the hydrolysates were evaporated to dryness under reduced pressure at 37° C to remove the hydrochloric acid. The dried residue was dissolved in distilled water to original volume, and some samples were neutralized to pH 8 with sodium hydroxide. The dissolved residues were sterilized by passage through a Seitz filter and cultured for sterility prior to use. Periods of hydrolysis which did not appear to completely destroy eliciting ability were chosen. This was done by removing aliquots of the hydrolysate at various times, neutralizing to pH 8 with NaOH, sterilizing by passage through a Swinney filter, and testing for eliciting activity on P. K. sites. This was done in an attempt to avoid complete hydrolysis which might destroy any hapten possibly produced by incomplete hydrolysis.

Some samples of ragweed extract were hydrolyzed at varying concentrations of hydrochloric acid after heating the ragweed extract to 56° for thirty minutes.

Enzymatic Digestion.—A review of the literature concerned with the ability of digestive enzymes to destroy the skin eliciting activity of ragweed extract reveals conflicting reports on this subject.[22-26] In our experiments, both tryptic and peptic digestion were carried out at the optimum pH for these enzymes.[27] Ragweed extract was digested with 3 per cent twice

TABLE II. MEASUREMENT OF THE NEUTRALIZING AND ELICITING ABILITY OF ALTERED RAGWEED EXTRACT

Method	Days Hydrolysis	Neutralizing Activity	Eliciting Activity
Acid hydrolysis			
10N	5	Absent	Absent
	10	Absent	Absent
	24	Absent	Absent
3N	2	Absent	Absent
1N	10	Absent	Absent
.1N	26	Present	Present
3N +heat	1	Present	Present
	2	Absent	Absent
	3	Absent	Absent
Trypsin	3	Absent	No end point
Pepsin	3	Absent	Absent
Trypsin +heat	3	Absent	Absent
Pepsin +heat	3	Absent	Absent
Dialysis	4 hours	Absent	Present
Freezing and thawing		Absent	No end point
Re-evaporation		Present	Present

recrystalized trypsin for three days at a pH of 8. Pepsin digestion was conducted for three days at a pH of 2, followed by neutralization of the hydrolysate to pH 8 with NaOH. Since both pepsin and trypsin are inactivated by autolysis, additional trypsin and pepsin were added to the hydrolysates at daily intervals for the three-day periods. Hydrolysis was discontinued at the end of this period because there was decreased eliciting activity of the ragweed extracts. Following the digestions, the hydrolysates were dialyzed against buffered saline through a Visking cellophane membrane to separate the enzymes from the dialysate used for testing.

Evaporation and Refreezing.—1:50 ragweed extract was evaporated to dryness under reduced pressure at 37° C and redissolved to original volume in distilled water. This was repeated five times. A separate sample was frozen and thawed sixty-seven times, with the resulting materials used for testing.

Dialysis Alone.—1:50 ragweed extract was dialyzed against buffered saline at pH 8 through a Visking membrane. Periods of dialysis were four, eight, sixteen, twenty-four seventy-two and ninety-six hours. The dialysates of all samples gave positive skin tests on P.K. sites, and the four-hour dialysate was used to test for haptenic activity.

The method of testing the altered extracts is shown in Table I and the materials prepared by the above methods which were tested for haptenic

activity are shown in Table II. Using this method, the ability of an altered extract to change the neutralizing and eliciting activity of a standard ragweed extract is compared with buffered saline to provide a constant dilution factor.

TABLE III. PERSISTENT NEUTRALIZING AND ELICITING ACTIVITY OF RAGWEED EXTRACT TREATED BY REPEATED EVAPORATION

	Neutralizing Activity		Eliciting Activity	
	Control	Treated Ragweed	Control	Treated Ragweed
Increasing serial four-fold dilutions of ragweed extract	−	−	+++	++++
	−	−	++	+++
	−	−	++	+++
	±	−	+	++
	+	−	+	++
	++	+	±	++
	++	+	±	++

Technique used is illustrated in Table I.

RESULTS

The results of measurement of the neutralizing and eliciting ability of the altered ragweed extracts are demonstrated in Table II. Both neutralizing and eliciting ability were destroyed by acid hydrolysis at 10N concentration and by 3N with or without heat, excepting for 3N HCl hydrolysis for twenty-four hours. This period of hydrolysis did not com-

TABLE IV. HYDROLYSIS OF RAGWEED EXTRACT AT 3N HCl FOR FORTY-EIGHT HOURS SHOWING COMPLETE DESTRUCTION OF NEUTRALIZING AND ELICITING ACTIVITY OF THE TREATED RAGWEED EXTRACT.

	Neutralizing Activity		Eliciting Activity	
	Control	Treated Ragweed	Control	Treated Ragweed
Increasing serial four-fold dilutions of ragweed extract	−	−	+++	+++
	−	±	+++	+++
	±	+	++	++
	+	+	++	++
	++	++	+	+
	++	++	±	±
	+++	+++	−	±
			Skin control ±	Skin control ±

pletely destroy the neutralizing or eliciting ability of the ragweed extract. Trypsin and pepsin digestion destroyed activity under the conditions used in the experiments. The four-hour dialysate of ragweed extract showed some eliciting ability but no detectible neutralizing activity was demonstrated. Repeated freezing and thawing destroyed the neutralizing activity, but repeated evaporation did not destroy the activity of the extract.

Table III illustrates the results obtained with repeated evaporation of ragweed extract. Both neutralizing and eliciting activity remain, and there is no significant alteration of the neutralizing : eliciting ratio of the control ragweed extract.

TABLE V. APPARENT INCREASE IN NEUTRALIZING ACTIVITY OF RAGWEED EXTRACT TREATED WITH 3N HCl FOR TWENTY-FOUR HOURS AFTER HEATING

	Neutralizing Activity		Eliciting Activity	
	Control	Treated Ragweed	Control	Treated Ragweed
Increasing serial four-fold dilutions of ragweed extract	±	±	++++	++++
	±	±	++++	++++
	±	±	++++	+++
	++	±	+++	±
	+++	±	+++	±
	+++	±	+	±
	++++	±	+	++

Table IV shows the results obtained with acid hydrolysis at 3N HCl for forty-eight hours with destruction of both eliciting and neutralizing activity of the treated ragweed extract.

The initial results obtained with certain acid hydrolysates were very encouraging. An example is shown in Table V. The material tested in this experiment was ragweed extract treated with acid hydrolysis at a con-

TABLE VI. EFFECT OF ACID ON THE NEUTRALIZING:ELICITING RATIO

	Neutralizing Activity			Eliciting Activity		
	Control (Buffered Saline)	Acidified Saline pH 2	Treated Ragweed pH 2	Control (Buffered Saline)	Acidified Saline pH 2	Treated Ragweed
Increasing serial four-fold dilutions of ragweed extract.	−	−	−	+++	+++	+++
	−	−	−	+++	++	+++
	−	−	−	++	++	++
	−	−	−	++	+	±
	−	−	−	+	−	±
	++	−	−	−	±	−
	+++	−	−	±	±	±

centration of 3N HCl for twenty-four hours after the extract had been heated to 56° C for thirty minutes. These results seemed to show definite neutralization with the hydrolysate and suggested that the extract contained neutralizing hapten. Although greater neutralizing activity was observed, there was actually a diminished eliciting reaction as compared with the control. A possible explanation for this was that the neutralizing hapten had greater affinity for reagin than the unaltered antigen in the control dilutions. Subsequent investigation, however, showed that although the hydrochloric acid had been removed by evaporation to dryness under reduced pressure, the resultant material had a pH of 2 after the hydrolysate residue was dissolved in distilled water. Following neutralization of these hydrolysates to pH 8 with sodium hydroxide, all apparent neutralizing activity disappeared. Consequently, an experiment was conducted to compare the neutralizing:eliciting ratio of reagin-standard ragweed extract mixtures, to which were added buffered saline acidified to pH 2 with HCl, unneutralized hydrolysate, or buffered saline at a pH of 8.

The results of this experiment are shown in Table VI. This showed that the apparent neutralizing ability of the hydrolyzed extracts with a final pH of 2 was not a result of haptenic effect but a function of acid concentration, since the acidified saline also "neutralized" the reagin completely. The most logical explanation for this "neutralization" seemed to be that the reagin was altered by the concentration of acid present in the hydrolysates.

TABLE VII. REACTIVITY OF P.K. SITES PLANTED WITH SERIAL DILUTIONS OF NEUTRAL AND ACIDIFIED RAGWEED REAGIN SERUM AND CHALLENGED WITH RAGWEED EXTRACT IN TWENTY-FOUR HOURS

Dilutions of Serum with Buffered Saline, pH 8		Dilutions of Serum with Buffered Saline Acidified to pH 2 with Hydrochloric Acid	
1:8	++	1:8	–
1:16	+	1:16	–
1:32	–	1:32	–
1:64	–	1:64	–

This hypothesis was tested by comparing the reactivity of passive transfer sites planted with serial dilutions of ragweed reagin in an acid solution with serial dilutions of ragweed reagin in a neutral solution. The results of this experiment are shown in Table VII and illustrate the alteration of reaginic activity by the acid diluting solution. Serum which was acidified to a pH of 2 with acidified saline, incubated for one hour and then neutralized to a pH of 8 with NaOH did not sensitize a passive transfer site. To determine whether acid altered post treatment "blocking antibody" in a manner similar to the effect on reagin, both were acidified, and no significant difference was observed between the effect of an acid concentration of pH 2 on reagin or blocking antibody.

DISCUSSION

A low molecular weight material existing naturally in ragweed extract or which can be produced by degradation of ragweed extract by various chemical or physical means would possibly have haptenic activity of great theoretic interest and therapeutic potential. Our method of testing for haptenic activity by measuring the ability of the treated ragweed extract to alter the neutralizing:eliciting ratio of control ragweed extract has proved to be a feasible modification of the passive transfer neutralization technique. An extension of this technique for use in comparative determinations of the degree of antigenicity in ragweed extract is under investigation.

We were unable to demonstrate haptenic activity in any of the materials utilized for testing. This does not exclude the possibility that such a material exists or may be produced.

Our results indicate that activity of ragweed extract is destroyed by pepsin and trypsin and by repeated freezing and thawing under the conditions of the experiments. Hydrochloric acid hydrolysis of ragweed extract

can destroy the activity of ragweed extract, but this destruction can be controlled by variation of the factors of time and acid concentration. Thus, the neutralizing and eliciting ability of ragweed extract is not destroyed in twenty-four hours, but in forty-eight hours in 3N HCl.

SUMMARY

A method is described which may serve to demonstrate the presence of haptenic activity in native or modified pollen extracts. By employing a modification of the passive transfer neutralization technique, the procedure measures the ability of the material under study to alter the ratio of neutralizing:eliciting activity of whole pollen extract.

No hapten-like material was found in unaltered ragweed extract, or in extracts treated by several chemical and physical methods to degrade the antigen. Degradation of ragweed extract under various conditions is described. Reaginic activity of serum is decreased by acid solutions. No difference was observed between the effect of acidity on "blocking antibody" and reagin.

REFERENCES

1. Landsteiner, K. L.: The Specificity of Serological Reactions, Revised Edition. Cambridge: Harvard University Press, 1945.
2. Landsteiner, K. L.: Experiments on anaphylaxis to azoproteins. J. Exper. Med., 39:631, 1924.
3. Heidelberger, M., and Kendall, F. E.: Studies on the precipitin reaction. J. Exper. Med., 57:373, 1933.
4. Tillet, W. S., Avery, O. T., and Goebel, W. F.: Chemo-immunological studies on conjugated carbohydrate proteins. J. Exper. Med., 50:551, 1929.
5. Benjamins, C. E., von Dishoeck, H. A. E., and German, J. W. M.: Studies on the active substance of grass pollen. I. activation of a small molecular weight active group through colloidal substances. J. Allergy, 6:335, 1934.
6. Long, W. I., and Teller, I.: Activation of ultrafiltrates of ragweed pollen extracts by means of colloidal substances. J. Allergy, 9:433, 1938.
7. Service, W. C.: Antigenic studies on polysaccharides isolated from pollen. Colorado Med., 34:468, 1937.
8. Pringle, Ross B.: The free amino groups of ambrosia elatior pollen proteins. J. Allergy, 24:251, 1953.
9. Newell, J. M.: A review of chemical studies on the allergens in pollens. J. Allergy, 13:177, 1941.
10. Loveless, M. H., Wright, W. I., and Ryan, A.: Allergenic fractions of low ragweed pollen. II. Some electrophoretic and chemical characteristics of diffusates. J. Allergy, 22:120, 1951.
11. Sherman, W. B., and Hebald, S.: The importance of certain antigenic fractions of ragweed pollen in relation to conditioned reactions during treatment. J. Allergy, 12:605, 1941.
12. Robbins, K. C., Samuels, A., and Mosko, M. M.: Chemical studies on a skin-reactive fraction from short ragweed pollen. J. Allergy, 19:35, 1948.
13. Perlman, Ely: Chromatographic analysis of ragweed pollen extract. Bull. New York Acad. Med., 27:586, 1951.
14. Abramson, H. A.: Chemical, physical and immunological properties of electrophoretically purified pollen extracts. Ann. Allergy, 5:19, 1947.
15. Abramson, H. A., Moore, D. H., and Gettner, J. J.: Electrophoretic and ultracentrifugal analysis of hay fever producing components of ragweed pollen extract. J. Physiol. Chem., 46:192, 1942.
16. Becker, E. L., and Munoz, L.: Multiplicity of antigens in Ragweed extract as demonstrated by the technique of J. Oudin. Proc. Soc. Exp. Biol. & Med., 72:287, 1949.
17. Stone, G. C. H., Harkavy, J., and Brooks, G.: Chemical investigations of giant ragweed pollen I. Ann. Allergy, 5:546, 1947.

18. Cooke, R. A., Stull, A., Hebald, S., and Barnard, J. H.: Clinical and serologic study of the relationship of great (Ambrosia trifida) and Los (Ambrosia artemisiifolia) ragweed pollen. J. Allergy 6:311, 1935.
19. Stull, A., and Sherman, W. B.: Further studies on the allergenic activity of protein and non-protein fractions of ragweed pollen extract. J. Allergy, 10:130, 1939.
20. Arbesman, Carl E., and Eagle, H.: The assay of ragweed pollen extracts. J. Allergy, 10:521, 1939.
21. Sheldon, J., Lovell R., and Mathews, K. P.: A Manual of Clinical Allergy. Philadelphia and London: W. B. Saunders Co., 1953.
22. Moore, M. B., and Unger, L.: Studies on pollen and pollen extracts. J. Allergy, 5:338, 1934.
23. Bernstein, C., Jr., and Kirsner, J. B.: Oral pollen therapy. J. Allergy, 8:221, 1937.
24. Thiberge, N.: The Effect of gastric digestion on the allergic power of pollen. New Orleans M. & S. J., 92:430, 1940.
25. Melli, G.: Sulla natura sostanze sensibilizzanti dei pollini. Reforma med., 43:511, 1927.
26. Farmer-Loeb, L.: Untersuchungen uber die Cheimische Natur der Allergene III. Biochem. Ztschr., 220:432, 1930.
27. Haurowitz, F.: Chemistry and Biology of Proteins. New York: Academic Press Inc., 1950.

The University of Michigan Medical Center

Submitted November 6, 1958

PHANTOM PROBLEMS

The world is teeming with problems. Wherever man looks, some new problem crops up to meet his eye—in his home life as well as in his business or professional activity, in the realm of economics as well as in the field of technology, in the arts as well as in science. And some problems are very stubborn; they just refuse to leave us in peace. Our agonized thinking of them may sometimes reach such a pitch that our thoughts haunt us throughout the day, and even rob us of sleep at night. And if by lucky chance we succeed in solving a problem, we experience a sense of deliverance, and rejoice over the enrichment of our knowledge. But it is an entirely different story, and an experience annoying as can be, to find after a long time spent in toil and effort, that the problem which has been preying on one's mind is totally incapable of any solution at all—either because there exists no indisputable method to unravel it, or because considered in the cold light of reason, it turns out to be absolutely void of all meaning—in other words, it is a *phantom problem,* and all that mental work and effort was expended on a mere nothing. There are many such phantom problems—in my opinion, far more than one would ordinarily suspect—even in the realm of science.—MAX PLANCK, *Scientific Autobiography,* Philosophical Library, 1949.

Papers of Interest

Rich, M., and Belle, M. S.: Agranulocytosis resulting from methimazole (tepazole). Report of three cases. J.A.M.A., 167:573 (May 31) 1958.
Although it is not certain that frequent leucocyte counts will anticipate production of agranulocytosis, they are recommended during administration of methomazole.

Schou, J.: The influence of cortisone on the subcutaneous absorption of drugs. Acta Pharmacol. et Toxicol., 14:251 (May) 1958.
Rapid rise in serum concentrations in cortisone-treated animals when sulfacetamide sodium in injected subcutaneously indicates enhancement of absorption rate.

Tokuda, S. and Weiser, R. S.: Production of anaphylaxis in the white mouse with soluble antigen-antibody complexes. Science, 127:1237 (May 23) 1958.
Discussion of the site at which primary cell anaphylaxis is produced by the action of antigen-antibody complexes.

Tullis, J. L.: Prevalence, nature and identification of leukocyte antibodies. New England J. Med., 258:12 (Mar. 20) 1958.
A simple test for the demonstration of antileukocyte antibodies is described. Chemical and electrophoretic study show that antileukocyte-antibody activity is made up of at least two components: one having the characteristics of a beta globulin and the other of an alpha globulin.

Sheard, C., Jr., Spoor, J. and Abel, R.: Contact dermatitis from "high-speed-duplicator" papers: a new disease of office workers. A.M.A. Arch. Dermat., 77: 435-437 (April) 1958.
In five patients, contact dermatitis was discovered to be due to sensitized paper of duplicating systems.

Rosenthal, A.: Follow-up study of fatal penicillin reactions. J.A.M.A., 167:9, 1118-1121 (June 28) 1958.
Emphasizes role of prior sensitization by fungous infections and unsuspected reactions perhaps due to ingestion of penicillin in milk.

Gross, E. R.: An oral antigen preparation in the prevention of poison ivy dermatitis. Indust. Med., 27:3, 142-144 (March) 1958.
Of 455 patients treated prophylactically 76.9 per cent reported they were "either free of ivy dermatitis or experienced milder attacks." Evidence that preparation given was directly responsible is not convincing.

Fink, M. A. and Gardner, C. E.: Anaphylaxis in guinea pig: improbability of release of serotonin in the Schultz-Dale reaction. Proc. Soc. Exper. Biol. & Med., 97:554-557, 1958.
Third of four conclusions states, "It was impossible to demonstrate the release of serotonin from sensitized guinea pig lung, uterus or ileum in the presence of highly serotonin sensitive mouse uterus."

Jordan, J. W. and Darke, C. S.: Chronic beryllium poisoning. Thorax, 13:69-73 (March) 1958.
Dyspnea and unproductive cough developed ten years after exposure. Because all patients show positive patch tests to beryllium the disorder is due to development of hypersensitivity.

Malten, K. E.: Occupational eczema in shoemakers resulting from use of a new type of glue. Nederl. tijdschr. geneesk., 102:268-272 (Feb. 8) 1958 (In Dutch).
Contact dermatitis due to a phenolformaldehyde synthetic resin. The primary sensitizing agent was probably p-tertiary butyl phenol.

Dickie, H. A. and Rankin, J.: Farmers lung. An acute granulomatous interstitial pneumonitis occurring in agricultural workers. J.A.M.A., 167:9, 1069-1076 (June 28) 1958.
Sensitivity to molds or their metabolites appears to be causative of a syndrome distinguished by dyspnea, cough, hemoptysis, fever, chills and weight loss. Exposure must be minimized.

Frantz, A. G.: Fatal jaundice associated with iproniazid (Marsilid) therapy. Report of a case. J.A.M.A., 167:8, 987-8 (June 21) 1958.
No comment.

Sturmer, F. C., Jr.: Antihistamines and diphenylhydantoin-induced gingival hyperplasia. New England J. Med., 259:10 (Sept. 4) 1958.
In 28 patients who received antihistamines for gingival hyperplasia thought to be due to administration of diphenylhydantoin sodium, no improvement was noted after a three-month course of therapy.

Juergens, J. L.: Side effects of antihypertensive drugs. Proc. Staff Meet. Mayo Clin., 33:12 (June 11) 1958.
The physician who treats hypertensive patients must be familiar with their side effects so that the best possible control of the blood pressure with the least possible discomfort to the patient may be obtained.

Speirs, R. S.: Advances in the knowledge of the eosinophil in relation to antibody formation. Ann. New York Acad. Science, 73:283, 1958.
Report on experiments leading to the hypothesis that the eosinophils take up antigen and produce the template. This, *via* phagocytosis of the eosinophils, is utilized by cells of the reticuloendothelial family for the production of antibody.

Galloway, W. H., and Mac Bean, L. M.: Generalized vaccinia in infancy. A report of four cases. Brit. Med. J., 2:490 (Aug. 23) 1958.
Generalized vaccinia may be due to failure of their resistance mechanism. Infants who develop cutaneous complications of smallpox vaccination should be given hyperimmune vaccinia gamma globulin and a wide-spectrum antibiotic.

Resch, C., and Evans, R. R.: Chronic urticaria and dental infection. Cleveland Clin. Quart., 25:167, 1958.
In 50 of 100 patients with chronic urticaria, chronic dental infection was present in 17 following treatment. The urticaria was unaffected in 11, relieved in 6, with relapse in one in three months, in a second in 11 months, and in the third, in 13 years.

Weber, G.: Urticaria-like reaction after x-ray treatment. J. Invest. Derm., 30:6, 1958.
Demonstration by means of Koenigstein-Urbach test that an antigen-antibody reaction is responsible for urticaria-like eruption following roentgen radiation.

Weigle, W. O.: The nature of antigen-antibody complexes formed in rabbits during an immune response to bovine serum albumin. J. Exper. Med., 107:653 (May 1) 1958.
The appearance of circulating antigen-antibody complexes and immune elimination of antigen may depend on the quantity of injected antigen and the rate of synthesis and quality of the antibody produced.

Kammerer, W., Freiberger, R., and Rivelis, A.: Peptic ulcer in rheumatoid patients on corticosteroid therapy. A clinical, experimental and radiologic study. Arth. & Rheum., 1:122 (Apr.) 1958.
Ulcers occur in patients who take large amounts of steroid. Corticosteroids may decrease resistance of the gastric mucosa. This more adequately explains the incidence of ulcer than does a postulated change in gastric secretion.

Paterson, J. L.: Expectorants and antitussives. Pharm. J., 180:311 (Apr. 26) 1958.
Review of physiological mechanism of cough, therapeutic agents and how to formulate them.

News Items

FLORIDA ALLERGY SOCIETY

At a meeting in Miami Beach on May 3, 1959, the Florida Allergy Society elected the following officers:

President.....James H. Putnam, M.D., Miami
Vice President and
President-Elect.....L. Irving Weintraub, M.D., Gainesville
Secretary-Treasurer.....Benjamin A. Johnson, M.D., Jacksonville

MICHIGAN ALLERGY SOCIETY

The officers of the Michigan Allergy Society for the year 1959-1960 are as follows:

President.....Milton J. Steinhardt, M.D., Detroit
Vice President.....Robert G. Lovell, M.D., Ann Arbor
Secretary.....Alex S. Friedlaender, M.D., Detroit
Treasurer.....Hilda Hensel, M.D., Munroe

WEST VIRGINIA STATE SOCIETY OF ALLERGY

The Second Annual Meeting of the West Virginia State Society of Allergy will be held on August 20, 1959, at 2:00 p.m., at the Greenbrier Hotel, White Sulphur Springs, West Virginia. This meeting will be a section of the 92nd Annual Meeting of the West Virginia Medical Association. The program will consist of three papers prepared by nationally prominent allergists, and a "wet clinic" on diagnostic method in allergy, which will be followed by a panel discussion on subjects of general interest in allergy.

Officers elected for 1959-1960 are as follows:

President.....Sarah L. C. Stevens, M.D., Huntington
Vice President.....Marshall Carper, M.D., Charleston
Secretary-Treasurer.....Merle S. Scherr, M.D., Charleston

SYMPOSIUM ON ANTIBIOTICS

The Seventh Annual Symposium on Antibiotics sponsored by the two MD Publications, *Antibiotics and Chemotherapy* and *Antibiotic Medicine and Clinical Therapy*, will be held at the Mayflower Hotel, in Washington, D.C., on November 4, 5 and 6, 1959. The registration fee is $1.00.

Abstracts must be submitted in triplicate by September 14, 1959, and should contain approximately 200 words typewritten and double spaced, to Henry Welch, Ph.D., Director, Division of Antibiotics, Food and Drug Administration, Washington 25, D.C.

The original manuscript and one copy must be submitted by October 15, 1959. No more than six illustrations should come with each manuscript, and glossy photographs if submitted should be no larger than 8½ x 11 inches. Bibliographies should conform to the style of the Quarterly Cumulative Index Medicus. Generic names of drugs should be used for other manuscripts excepting the first time the drug is mentioned, in which case the trade name may be referred to in a footnote.

In Memoriam

MAURICE S. FOX

Maurice Simpson Fox was born February 4, 1901, the son of Doctor and Mrs. Richard Fox of Freelandville, Indiana. His father practiced medicine for fifty-eight years. He graduated from grade and high school in Freelandville, Indiana, and received his B.S. degree from Indiana University in 1928 and his M.D. in 1930. He taught English and Science in the high school in Freelandville, Indiana, for five years. He served his internship and residency at the University Medical Hospitals.

In 1931, he married Esther G. Keeling, R.N., and is survived by her and two children, Mrs. Kenneth Thornberry, a teacher at Lombard, Illinois, and a son, Richard, of Indianapolis, a student in the Indiana University Dental School, as well as by a sister, Mrs. J. E. Welton, a teacher in a Vincennes school, and three grandchildren.

Dr. Fox was an officer of the United States Coast Guard Auxiliary and commandant of a flotilla. He was a member of the American Medical Association, Indiana State Medical Association, a Fellow of the American College of Allergy, American Academy of Allergy, and a member of the International Correspondence Society of Allergists. He was on the staff of Good Samaritan Hospital of Vincennes where he was an instructor in allergy and dermatology, Lawrence County Hospital of Lawrenceville, Illinois, and Davies County Hospital of Washington, Indiana. He also taught at the School of Nursing, Vincennes. He was a Captain in the Medical Corps in World War II but was retired because of a coronary attack in 1943 and returned to Vincennes, limiting his practice to allergy since 1945.

Dr. Fox was very active in Masonic circles belonging to the Masonic Lodge, Scottish Rite and Shrine. He was also a member of B.P.O.E.

Following his coronary attack in 1945, Dr. Fox developed a cardiac infarct and was hospitalized last August. He died of coronary thrombosis on November 21, 1958.

His many friends in the College join in extending their sincere sympathy to his family in their sorrow.

—F.W.W.

THE NEUROSES

"I regret that here and there I must criticize some of the practices of the profession which I love, but I cannot tell what I think are desirable improvements without first pointing out those practices of ours which have proved to be mistaken and unfortunate. Some of the things I say here I would not have dared say thirty-five years ago, but as Montaigne wrote, as a man grows older he should gain courage to express ever more of the truth as he sees it. Also, as he approaches three score and ten he should feel ever less concern over whether other men disagree with him, or like what he says. If in his consultant practice he sees what the common medical mistakes are, it is his duty to warn against them. All that need concern him is that he speak truly and kindly and humbly, and with a full realization of the fact that in his ignorant youth, he made most of the mistakes which he now asks his readers to avoid."—WALTER C. ALVAREZ, M.D., *The Neuroses*, W. B. Saunders Company, 1953.